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OBSERVATIONS ON THE RESPIRATORY GASES IN VENTRICULAR PAROXYSMAL TACHYCARDIA

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Recently a study of the blood gases in a case of paroxysmal tachycardia [2] was published from this laboratory, in which a definitely increased oxygen unsaturation of the hemoglobin in arterial blood was found to be present during the paroxysms of tachycardia. The present case is reported because a similar observation was made.

Report of Case

H. J. D., a man aged 32 years, complaining of attacks of rapid heart action, was admitted to the hospital on May 2, and discharged on July 20, 1923. Four or five years before the patient had had a mild attack of acute rheumatic fever. There was no history of sore throats or of chorea. In the summer of 1921 the patient had a brief attack of palpitation and marked weakness. In Feb., 1922, there was a similar attack and since June, 1922, he has had many. The attacks come on suddenly, usually after strenuous effort. They are characterized by weakness, palpitation, mental distress, nausea and vomiting. The patient has never lost consciousness. The pulse has repeatedly been observed to be exceedingly rapid. The attacks last from one to 18 hours and end spontaneously, frequently with vomiting. No measure tried has consistently prevented or terminated the attacks. In the intervals the patient is free from symptoms. The general physical examination was entirely negative except that there was moderate undernutrition. The tonsils were normal. There was slight cardiac enlargement (the relative cardiac dullness measured 10 cm. to the left in the fifth interspace and 3 cm. to the right in the fourth interspace). There was no thrill or murmur. The pulse rate was 80; there was no irregularity. The blood pressure was 125/75. There was no sign of heart failure. The blood and urine were normal. The blood Wassermann re-

action was negative. Teleoroentgenographic measurements of heart were: M. L. 9.5 cm. and M. R. 4 cm. The patient's vital capacity was 87 per cent of the calculated normal value. The diagnosis was rheumatic heart disease with paroxysmal tachycardia of ventricular origin.

During his stay in the hospital the patient had six paroxysms of tachycardia. These attacks all began and ended suddenly. The shortest lasted four hours and the longest 28 hours. The pulse ranged from 180 to 220 in various attacks. At times a slight irregularity of rhythm was perceptible on auscultation over the heart. No pulse deficit was made out. Vagal and ocular pressure were repeatedly without effect on the rate. With the onset of an attack the patient experienced marked epigastric discomfort, palpitation and dizziness. He became so weak that he remained in bed perfectly still. As the attack progressed he became dyspneic and showed moderate general cyanosis. No râles were ever heard over his lungs, but it was not thought justifiable to move him toward the end of the longer paroxysms, as his condition then seemed precarious. A teleoroentgenogram taken during the early part of an attack showed no increase in the size of the heart. The vital capacity fell to 60 per cent of the calculated normal. The blood pressure was as low as 75/60 in one attack and immediately after the cessation of the paroxysm was observed to return to 120/80.

Despite the patient's statement that he was free from symptoms between the attacks of tachycardia, he showed very definite limitation of his activity in the intervals while in the ward.

Digitalis and quinidin (separately administered) neither prevented nor terminated the paroxysms. Prolonged absolute rest in bed was followed by a diminution in their frequency and severity, and the patient finally left the hospital after having been free from attacks for six weeks.

Electrocardiographic Records

Fig. 1 is a record secured during one of the longer paroxysms of tachycardia. Records of other attacks were essentially similar. The rate is 206 and the rhythm is regular. No P waves are discernible except in Lead III in which they are distinctly shown. It will be noticed that occasionally the P waves are missing in this lead. On account of the duration of the attacks no record of an offset was secured, and because of their severity it was not thought justifiable to attempt to initiate a paroxysm. It was suspected that the records secured were those of ventricular tachycardia, but as a rule it is impossible to make this diagnosis from the simple record of an attack. Fig. 2, however, makes it certain that such is the correct diagnosis, for it shows clearly that at this time the ventricles were contracting twice for each auricular contraction. The P waves appear distinctly as notches upon alternate T waves. This can be explained only by the existence of a retrograde mechanism with 2:1 ventriculo-auricular block. On this basis Lead III of Fig. 1 shows occasional dropped beats. It is of interest in this connection that one paroxysm was terminated by a brief period of auricular fibrillation, a mechanism which was not observed in the patient at any other time.

It is not easy to say in which ventricle the abnormal mechanism may have arisen because Leads I and II are both negative and the electrical axis lies in the neighborhood of minus 150°, which is midway between the regions ordinarily assigned to the dextro- and levo-cardiograms.

Further strength is lent to the diagnosis of ventricular tachycardia by the occurrence of ventricular premature beats of the form of the ventricular complex in the tachycardia. Fig. 3 shows the normal mechanism of this patient in the three leads (records taken on different occasions are assembled to show the premature contractions). In each lead there is a premature ventricular beat, the outline of which is similar to that present during the paroxysms. The P-R interval is normal (0.16 sec.). The QRS interval is increased (0.13 sec.). The T waves in Leads I and II are opposite in direction to the initial ventricular waves. The curves suggest the existence of partial right bundle branch block. It is interesting to note that if the tachycardia is interpreted as arising on the right side, its origin is then on the side which is normally partially blocked.

Strong and Levine [8] have recently called attention to the occurrence of much greater irregularity in paroxysmal tachycardia of ventricular origin than is present when the arrhythmia arises in the auricle. Feil and Gilder [3] found that in auricular tachycardia the difference in cycle length is rarely as great as 0.01 sec. In the present case variations in cycle length of 0.04 sec. occur and variations of 0.02 sec. are frequently present.

Fig. 4 shows a bigeminal rhythm due to ventricular premature beats, with distinct retrograde P waves. This is an unusual mechanism, since ventricular premature beats do not as a rule disturb the dominant rhythm.

Respiratory Observations

Table I gives the data secured upon examination of the respiratory gases, including those of the blood, in the presence of the normal mechanism and of the tachycardia. The blood gases were determined by the methods of Van Slyke, the usual precautions being observed in obtaining and handling the blood. Complete determinations of the basal metabolism were done, a Tissot spirometer being employed, and the respiratory gases were analyzed by standard Haldane methods.

The observations during the normal periods showed no abnormality. In both attacks of tachycardia in which an examination was made, the arterial blood showed a definite decrease in oxygen saturation (normally this is not under 90 per cent at the least). The attack of May

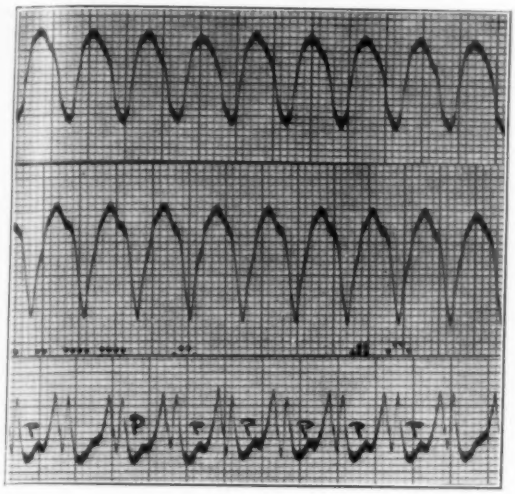

Fig. 1.—Electrocardiogram, May 25. Leads I, II and III. Paroxysmal tachycardia. Rate 207. P waves as marked in Lead III are occasionally missing.

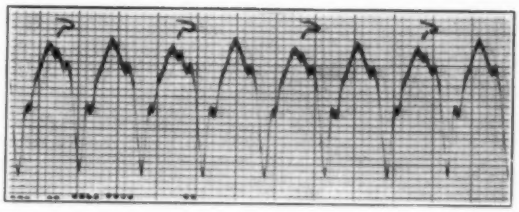

Fig. 2.—Electrocardiogram, Lead II, taken later during paroxysm shown in Fig. 1. P waves are distinctly shown as notches upon alternate T waves. This record shows that the mechanism was retrograde, with 2:1 block.

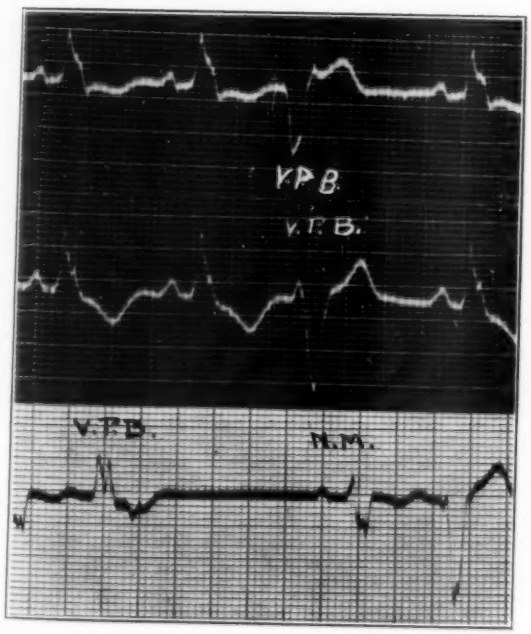

Fig. 3.—Electrocardiogram, Leads I, II and III, taken at different times, brought together to show ventricular premature beats of the form of the complexes in the paroxysms. Normal mechanism. Partial right bundle branch block. (Leads I and II, bromide paper. Lead III, film.)

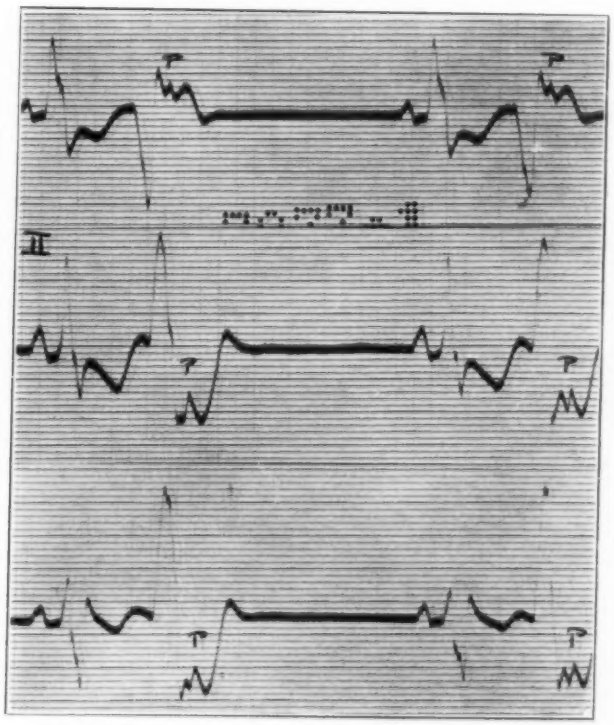

Fig. 4.—Electrocardiogram, Leads I, II and III, May 28. Bigeminal rhythm due to ventricular premature beats with retrograde auricular excitation. (Time intervals in 1/50 and 1/10 sec.)

3 was the more severe and the venous oxygen saturation was low. The patient showed general cyanosis. The increase in oxygen-combining power in the presence of the paroxysms suggests the possibility of concentration of the blood. The arterial carbon dioxide was definitely lowered during the tachycardia.

The respiratory rate and minute volume showed an increase during the attack. The changes in the composition of the expired and of the alveolar air were perhaps hardly significant. There was a slight but definite rise in basal metabolism.

DISCUSSION

The reported cases of ventricular paroxysmal tachycardia together with the criteria proposed for its diagnosis may be gathered from the recent articles of Wolferth and McMillan [9] and of Scott.[7]

This case is in sharp contrast to that reported by Scott in that quinidin therapy was entirely ineffectual, whereas in Scott's case "quinidin exercised a specific effect in controlling the tachycardia." The dosage and method of administration were the same; and the same drug used in this case was effective in causing reversion from auricular fibrillation to normal mechanism in other patients. The failure of this case to react to quinidin therapy probably has the same basis as in similar failures in the treatment of auricular fibrillation.

Levy [4] has noted the frequent occurrence of bundle branch block, ventricular premature beats and ventricular tachycardia as a toxic effect of quinidin in cases of auricular fibrillation which are unsuccessfully treated. The bigeminal rhythm shown in Fig. 4 appeared during the administration of quinidin and disappeared when the drug was withdrawn. However, it should be emphasized that the partial bundle branch block in the normal mechanism of this patient was constantly present and that the tachycardia occurred without reference to the administration of quinidin.

The attacks of tachycardia in this patient were accompanied by a degree of prostration unusual in auricular paroxysmal tachycardia. The most significant objective finding was that of a decrease in oxygen saturation of the arterial blood. No entirely satisfactory explanation of this observation can be offered, especially since there were at the time no out-spoken signs of congestion of the lungs. There was, however, a significant reduction in the vital capacity, which can only be explained by supposing that there was some degree of stasis in the pulmonary circulation. There is good reason to believe that in such a case as the present the circulatory minute volume is decreased, a change which may have a deleterious effect upon the pulmonary epithelium.

The observations by Barcroft [1] and by Meakins [5] of normal oxygen saturation of arterial blood in the presence of a rapid tachycardia may possibly be explained by the fact that they were dealing with relatively normal hearts. In the case reported by Carter and Stewart and in the present case there was undoubtedly marked myocardial damage. Barcroft's subject showed no evidence of disease and Meakins' work was experimental on normal dogs.

Peabody, Wentworth and Barker [6] found an average increase in basal metabolism of 12.8% in 14 patients with heart failure. The change in metabolic rate found in their series of patients ranged from minus 6 per cent to plus 40 per cent. The subject of this report showed an increase of 16.7 per cent during an attack of tachycardia. It seems likely that this increase may have been due to the added work of the heart and lungs rather than to some more fundamental change.

SUMMARY

A case of paroxysmal tachycardia of ventricular origin with retrograde mechanism is reported. No method of preventing or terminating the attacks was found. Quinidin therapy was apparently followed by an unusual bigeminal rhythm due to ventricular contractions which were followed by the auricles. During the paroxysms retrograde heart block sometimes appeared.

There was a definite decrease in the oxygen saturation and in the carbon dioxide content of the arterial blood in the presence of the tachycardia. The basal metabolism in one paroxysm was elevated 16.7 per cent. The respiratory gases and basal metabolism were normal during the normal cardiac mechanism.

TABLE I.

	Date		
	May 3	May 7	May 16
Cardiac mechanism	Paroxysm	Normal	Paroxysm
Respiratory rate	28	22	28
Resp. min. vol.	11,000 c.c.	8,900 c.c.	
Expired air—O_2	18.32%	18.03%	
Expired air—CO_2	2.05%	2.25%	
Alveolar air—O_2		12.80%	13.40%
Alveolar air—CO_2		6.00%	5.67%
Basal metabolism	16.7%	1.6%	
Oxygen capacity	21.80 vols. %	19.48 vols. %	20.76 vols. %
Oxygen saturation			
arterial	85.13%	94.50%	86.00%
venous	26.10%	60.47%	55.00%
Carbon dioxide content			
arterial	39.73 vols. %	51.04 vols. %	43.41 vols. %
venous	49.68 vols. %	53.18 vols. %	49.06 vols. %

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MENINGEAL RELATIONS OF THE HYPOPHYSIS CEREBRI

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General descriptions of the relations of the leptomeninges fail in every instance to make more than the most casual reference to the possibility of their having any definite distribution around the hypophysis cerebri in the sella turcica. The usual impression gained from brief descriptions in textbooks of Anatomy, or even more detailed observations in the literature, is that the arachnoid membrane is simply pierced by the infundibular stalk and that it has no anatomical relation whatever with the body of the hypophysis. For it is usually stated that the gland lies surrounded by the diaphragma sellae and the dural lining of the sella turcica itself.

Brief mention of a few references on this subject may be of interest. Haller,[4] in dealing with the physiology of the pituitary gland, asserted that the secretion is poured into the subdural space. The application of this latter term in referring loosely to either the subdural or the subarachnoid space was quite general at the time of Haller's publication. He did not state, however, whether he had any anatomical basis for such a statement, even supposing that his physiological observations were correct. Reichert[9] considered the pars anterior as a "proliferation of the cells of the pia mater," but this statement was probably not made with any idea as to an arachnoid covering.

Key and Retzius[8] in legends of their splendid plates describe the extent of flow of their injection mass in the subarachnoid space as follows:—Tafel VII, Fig. 1: "Around the peduncle of the hypophysis can be seen the injection mass which has gone through the dura and spreads out between the hypophysis and arachnoid which spans the sella turcica." Fig. 2: "In the cross-section of the hypophysis one sees on its upper surface, between it and the dura which bridges it, that the injection mass has penetrated the space as in the preceding figure." These injections were made into the subarachnoid space, and in order that the injection mass could have extended beneath the diaphragma sellae the space itself must have been continued through the opening in the diaphragm, provided that no membranes were ruptured. This point the authors failed to appreciate. Further extension was probably prohibited by the density of the mass itself.

Dandy and Goetsch,[3] in studies on the blood supply of the pituitary body, speak of having removed "a block of tissue containing the hypophysis and its meningeal envelope intact." And Cushing[2] says: "This combined neuro-epithelial structure becomes enveloped in an adherent dural capsule and occupies the sella turcica. The dural capsule in man has an upper diaphragm which stretches from the four clinoid processes and is perforated for the passage of the infundibular stalk." Herring[5] mentions the "subdural space" and speaks of lymph spaces which are frequently seen in the dura mater below the pituitary body. Holt[6] remarks that "as is well known, these membranes (arachnoid and dura) form a collar—the diaphragma sellae about the neck of the hypophysis—this collar is pierced by the infundibular stalk and the pars tuberalis." Atwell[1] in his extensive study on the embryology of the gland states that "in rabbits at birth the pars tuberalis lies in the pia mater of the floor of the brain except for a strong connection which unites it with the anterior lobe proper, this passing through the dura mater;" and again, "the pars tuberalis lies in the pia mater of the brain floor, the arachnoid spaces being located between it and the dura mater."

It is obvious that from these general statements no clear idea as to the exact distribution, if any, of the arachnoid and pia in relation to the gland itself can be gained, and further it might be said that the impression of a simple dural investment of the gland is the generally accepted one.

In order that an investment of the gland by the leptomeninges and their enclosed subarachnoid space may be anatomically possible, one embryological requirement must be fulfilled,—that is, the complete separation of the stalk of Rathke's pouch from the buccal cavity before the central nervous system has become completely surrounded by the mesenchymal cells destined to form the arachnoid and pia mater. This fact established, the continuity of the subarachnoid space both anatomically and physiologically remains to be demonstrated. These conditions have been complied with in every detail and set forth briefly in a preliminary report by the author[7] before the American Association of Anatomists.

In a 6 mm. pig embryo Rathke's pouch is simply an angular evagination of ectoderm; the infundibular portion of the hypophysis is here entirely lacking except for a possible indication of its presence as shown by a thickening of the lower wall of the ventricle which is in apposition to the buccal pouch. In the 9 mm. embryo (Fig. 6) development has progressed considerably, and mesenchymal cells can be seen extending down around the region

of the infundibulum and indeed separating the two elements of the gland except where they are directly applied to one another. At 12 mm. (Fig. 7) the connection between the pouch and ventricular wall is remarkably close and all mesenchymal cells have, as it were, been pushed aside. The layer of mesenchyme cells is rapidly becoming much more dense. In the 15 and 17 mm. embryo (Figs. 8, 9) conditions are very little changed with the exception of the stalk of Rathke's pouch. This has now become simply a double layer of cells (Fig. 9), as if pushed tightly together by the rapidly increasing mass of the mesenchymal cells. In the 19 mm. stage (Fig. 10) the stalk amounts to little more than a single strand of cells, and at 21 mm. (Fig. 11) this has finally disappeared entirely and the mesenchyme now completely surrounds the isolated pouch. In a reconstruction of a human embryo of 21 mm. in the Embryological Laboratory of the Carnegie Institute (Carnegie Collection, Embryo No. 460), study of the buccal surfaces shows that the stalk of Rathke's pouch has become entirely separated from the mouth cavity. The time of development in the two types of embryo is therefore apparently identical.

In Weed's [10] extensive studies on the development of the subarachnoid space we have valuable information which can be applied to the present problem. In his discussion of the appearance of the outer intact membrane of the arachnoidea he says: "This portion of the arachnoidea (which might be termed the arachnoid membrane as distinguished from the arachnoid trabeculae) first appears as a distinct line of mesenchymal condensation separating the mesenchyme into the primitive arachnoid and dura as in Figs. 76 and 77 d.m.c., Plate XIII (Embryo pig 32 mm.)."

We do not have, therefore, a complete investment of the central nervous system in the pig embryo by a definite arachnoid membrane until the 32 mm. stage, or until the embryo has increased in length 10 mm. over the size found to represent the point at which complete separation of Rathke's pouch took place. Practically the same conditions obtain in the human embryo in regard to the development of the arachnoid as in the pig. Consequently, from an embryological standpoint the complete investment of the hypophysis by the leptomeninges and subarachnoid space is entirely possible. There remains to be demonstrated the continuation of the pia and arachnoid and the patency of the cavum subarachnoidiale about the entire gland. This problem was investigated in adult dogs and cats, the material being controlled by serial sections of the hypophysis and its membranous coverings.

Two types of injection of the subarachnoid space were employed in addition to actual dissections of the hypophysis in the pig embryo. In the first type of injection advantage was taken of the fact, first demonstrated by Weed and McKibben,[11] that the cerebrospinal fluid pressure can be reduced below zero by the intravenous injection of a hypertonic solution of sodium chloride, provided the skull remained intact. A preliminary cistern puncture through the occipito-atlantoid ligament was made and this needle connected with a manometer filled with a solution of iron-ammonium citrate and sodium ferrocyanide. A 30% solution of sodium chloride was then injected intravenously, and as the cerebrospinal fluid pressure became markedly reduced, the solution in the manometer was sucked into the subarachnoid space. Rapid fixation of the brain was obtained by injection of 10% formalin solution through the aorta, while precipitation of the foreign salts *in situ* was effected by adding to the formalin a sufficient quantity of concentrated hydrochloric acid. This prompt fixation and precipitation does away with any possibility of diffusion of the salt, and when the precipitate is found by microscopical examination, the granules represent the actual position of the salt at the time of the animal's death. It will be seen from the above description that the decreased pressure of the cerebrospinal fluid draws the ferrocyanide solution into channels which may possibly not function actively under normal pressure conditions, but which must necessarily represent a direct continuation of the subarachnoid space itself.

The second method of injection was a simpler one but equally effective, and represented the opposite possibility in the matter of bringing into function any potential subarachnoid space in the region of the hypophysis. Here the solution was injected through the cistern needle under pressures greater than normal. After the preliminary puncture the normal pressure was established by observation for a few minutes and the foreign salt then introduced usually at an increase in pressure of 50 to 80 mm. of the fluid. The results obtained from the two methods were practically identical. Ordinarily when the solution is introduced simply by replacement (that is, at the animal's normal cerebrospinal fluid pressure), the circulation of the fluid is not active enough to carry it around the body of the hypophysis.

Complete serial sections were then cut of material prepared in this way and subjected to careful microscopical study and analysis. Previous examination of normal adult hypophyses, removed with all the investing membranes intact, showed between the dura and gland substance a definite double layer of mesothelial cells, but no actual space could be demonstrated. However, under the influence of either a reduction or an increase of the cerebrospinal fluid pressure, the existence of a definite subarachnoid space was readily made out and the arachnoid and pial membranes clearly outlined by the precipitated Prussian blue granules. Many obstacles to the free circulation of the fluid in this region present themselves, but under the influence of changes in pressure the injection mass could always be demonstrated as completely surrounding the gland.

At the anterior and posterior poles the subarachnoid space broadens out to form a triangular-shaped cistern the apex of which is pointed toward the base of the gland (Fig. 1). Encountering the clinoid processes the arachnoid and pia are brought into close apposition one with another, but continue intact around the bony projections and can easily be seen to contain the granules of the precipitated salt. On the base of the gland the two membranes still lie close together, but the space here is perfectly definite and is always filled with the dye. Great difficulty was experienced in keeping an intact arachnoid, owing to its very close association with the dura lining the sella turcica. Dissection of the bony floor of the sella, preparatory to the cutting of sections, frequently resulted in a tearing of the delicate membrane, and in addition it was sometimes torn during the cutting of sections. Sufficient care, however, resulted in the preparation of material in which the membrane remained intact. In the dog and cat the diaphragma sellae does not invest the infundibular stalk so closely as in man, particularly on the posterior surface, but even at the anterior pole the subarachnoid space is clearly formed by a reflection of the membrane around the infundibulum, thus maintaining its continuity.

Furthermore, these Prussian blue granules under either type of injection may be traced actually into the substance of the gland itself. Entering the perivascular spaces the precipitate can be followed into the stroma of the pars buccalis, outlining in many instances with great completeness the cellular columns of this portion of the gland. The great vascularity of this buccal portion of the hypophysis therefore offers an intimate association between the blood stream and the cerebrospinal fluid at this point. Granules can also be traced into the pars intermedia and even the pars nervosa, but never to the extent that is seen in the pars buccalis. In addition we have a definite passage through the substance of the pars tuberalis of Atwell.

In Fig. 1 a general idea of the shape of the gland can be obtained, with the arachnoid and pial membranes applied closely to its anterior and posterior portions; the dura mater was separated somewhat from the base of the gland during its removal from the sella turcica. Fig. 2 shows the subarachnoid space filled with granules investing the posterior pole, while Fig. 3 demonstrates the same condition holding true for the anterior portion. Here the space is clearly outlined as it lies beneath the floor of the ventricle and is reflected over the pars anterior. Its continuation around the clinoid process (in the dog, a cartilaginous structure) can be followed by the delicate line of Prussian blue granules, demonstrating clearly that under the conditions of injection described above even this extremely small space is at all times patent. Fig. 5 shows the extent of the space at the base of the gland and the meningeal layers can be distinctly made out. Fig. 4 represents a somewhat higher power view of the pars buccalis, the single layer of cells of the arachnoid and pia enclosing a space of considerable extent filled with the dye granules and here too the extension of the injection mass into the stroma of the gland itself is quite obvious. This particular injection was made by the second method described, that is, at a pressure of 50 mm. of fluid above the animal's normal level.

Conclusions

1. The stalk of Rathke's pouch disappears before the brain has become completely surrounded by its meningeal coverings in the embryo, thus making the investment of the hypophysis cerebri by the subarachnoid space developmentally possible.

2. The complete investment of the hypophysis by the subarachnoid space in dogs and cats has been demonstrated by two methods of injection either by suction, where the cerebrospinal fluid pressure has been reduced to below zero, or at an increase of 50-80 mm. of fluid above normal.

3. Passage of fluid from the subarachnoid space into the substance of the gland has also been shown under these same conditions.

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LEGENDS FOR FIGURES

Fig. 1.—Sagittal section of hypophysis of adult dog.

Figs. 2, 3, 4, and 5.—Details of hypophysis showing Prussian blue granules in subarachnoid space and in substance of pars buccalis.

Figs. 6, 7, 8, 9, 10, and 11.—Sagittal sections through Rathke's pouch in embryo pigs from 9 to 21 mm. in length (see text).

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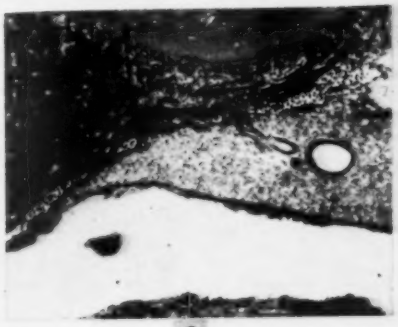

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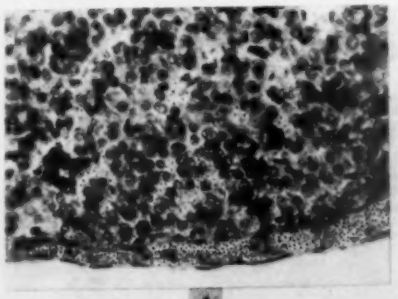

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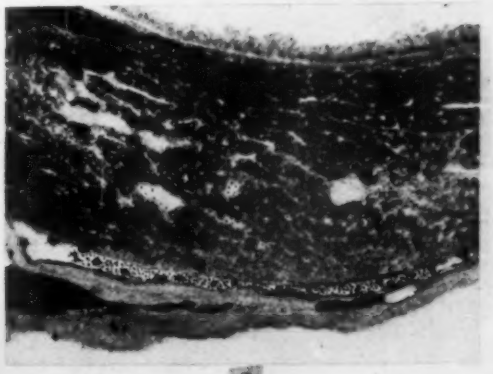

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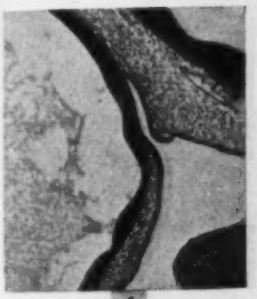

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SYPHILITIC ARTHRITIS WITH EOSINOPHILIA: RECOVERY OF T. PALLIDUM FROM THE SYNOVIAL FLUID*

By ALAN M. CHESNEY, M. D., JAROLD E. KEMP, M. D. and WILLIAM H. RESNIK, M. D.

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The purpose of this communication is two-fold: (1) to record two cases of syphilis showing an unusual clinical syndrome; (2) to record the recovery of *T. pallidum* from the synovial fluid of one of these patients in whom there was an acute hydrops of the knee.

CLINICAL OBSERVATIONS

These two cases came under observation in the Medical Clinic of the Johns Hopkins Hospital within a few weeks of one another. The reaction which they presented to the syphilitic infection was so unusual and so strikingly similar in each instance that they have been deemed worthy of report.

In brief, the syndrome presented by each patient was as follows: (a) marked enlargement and tenderness of all the lymph glands accessible to palpation, (b) acute polyarthritis, (c) eosinophilia, (d) a positive blood Wassermann reaction, (e) fever, (f) prompt recovery under antisyphilitic treatment. In one patient the spleen was enlarged and there was an accumulation of fluid in both knee-joints.

Space is not available for a discussion in this place of the question of syphilitic arthritis. However, it may not be amiss to say at this point that a survey of the literature has not disclosed any mention of just this type of reaction (arthritis with eosinophilia) to syphilitic infection. If it has been recorded previously, we have failed to find it.

We are indebted to Dr. James R. Cash of the Department of Pathology, for descriptions of the glands removed from both patients.

The histories of the cases follow. Only the important findings will be recorded.

CASE 1

L. D.—Female. Colored. Age 23. Married. Housewife. Service No. 50596.

Admitted.—Johns Hopkins Hospital, January 7, 1924. Discharged, February 2, 1924.

Complaint.—"Pains in joints for two months."

Family History.—Married four years, no children, an indefinite history of an early abortion. Her husband had been a patient in the syphilis clinic of the J. H. H. Dispensary about two years before marriage to the patient. He was known to have had a positive Wassermann reaction in October, 1917, and as late as February, 1924, after the onset of his wife's illness. During the interval 1917-1924 he received very scanty treatment for syphilis.

Past History.—Her general health had been excellent. She did not recall ever having been ill with an acute infection. A complete review of the patient's past history revealed no other facts of importance. There was no history of the usual early manifestations of syphilis.

Present Illness.—About two months before admission there was a rather sudden onset of stiffness and pain in the neck, shoulders and knees, and the patient was obliged to go to bed shortly afterwards. About a month later her throat became sore, and large, tender, painful nodes appeared beneath the jaw. She failed to improve under her physician's care and visited the Out-Patient Department on January 3, 1924, where she was examined in the orthopedic, laryngologic and syphilis clinics. The findings were essentially the same as those in the Hospital and will be described below. She was admitted to the Hospital on January 7, 1924.

Physical Examination.—On admission, temp. 98.2° F., pulse 76, respirations 20, B. P. 110/60. The patient was well nourished, did not appear acutely ill, but there was evident discomfort on movement of the head or limbs. There was a marked general lymph glandular enlargement. The glands varied in size from 0.2-0.3 cm. to 1.0-3.0 cm. in the long diameter; they were smooth, firm, discrete, markedly tender, freely movable in the surrounding tissue. Examination of the head was negative except for slight enlargement and injection of the tonsils. The thyroid was slightly and diffusely enlarged and the isthmus was somewhat tender. The liver and spleen were palpable, apparently of normal consistence, not tender. Pelvic examination was entirely negative. There were pain, tenderness, and limitation of motion of the temporomandibular, sternoclavicular, acromioclavicular, knee and left ankle joints. In addition, there was swelling of both knee joints and evidence of a small amount of fluid in each. About none of the joints was there any redness or localized heat. On the outer third of the left clavicle there was a point of exquisite tenderness. The reflexes were normal. The skin and mucous membranes showed no evidence of syphilis.

Laboratory Findings on Admission

Blood.—		Differential count	
R.B.C.	5,120,000	P.M.N.	72%
W.B.C.	7,040	P.M.E.	10%
Hb (Sahli)	90%	Lymph.	10%
		L. M. Trans.	8%

*Read before the Johns Hopkins Hospital Medical Society, April 7, 1924.

Stained smears showed nothing abnormal.

Urine.—Negative.

X-Ray Report.—January 7, 1924. (Dr. Pierson):—Right shoulder negative. Collection of fluid in knee-joints. No changes in bones present.

Blood Wasserman.—Complete fixation with all antigens.

Stools.—(Repeated examinations) Negative for ova or parasites.

Blood Chemistry.—The non-protein nitrogen, sugar and CO_2 combining capacity were normal.

Phthalein Test.—(Intramuscular injection) 50% output in two hours.

Clinical Course.—The patient was put to bed and given anodynes. Under this regime the symptomatic improvement was relatively slight; there was no objective change in the arthritis and a second blood count showed an eosinophilia of 7%. Four days after admission an inguinal gland was removed for histological study and inoculation into rabbits, and at the same time the right knee-joint was aspirated. About 20 c.c. of cloudy yellow fluid were recovered, which clotted in about an hour. Examination of this fluid showed 17,650 white cells per c. mm. Of these the majority were lymphocytes. Dark field examination was negative for T. pallidum.

On the following day (January 12, 1924) antisyphilitic treatment was begun, 0.4 gm. of neoarsphenamine being given intravenously, followed on January 14, 1924, by an intravenous injection of 0.2 gm. of arsphenamine. Mercury inunctions and potassium iodide by mouth were commenced at the same time. By January 16th, four days after specific treatment was begun, there was a distinct clinical improvement. The lymph nodes had appreciably decreased in size and were no longer tender. The pain and tenderness of the joints had entirely disappeared. A small amount of fluid remained in the knee-joints but this was soon absorbed. The spleen could not be felt. Following the administration of the arsphenamine, the temperature, which had ranged between 98.6° and 100.5° F., dropped slightly, and up to the time of her discharge from the Hospital varied from 98°-99.5°, with an occasional rise to 100° F. The eosinophiles decreased to 1% after the second dose of arsphenamine. Cerebrospinal fluid obtained after the second dose of arsphenamine gave the following results on examination:

Cells	4 per c. mm.
Globulin	0
Wassermann	Negative
Colloidal mastic reaction	Negative

From time to time a friction rub was audible in the left axilla. An x-ray of the lungs, taken on January 8, 1924, showed an increased amount of fibroid infiltration, non-tuberculous. Because of the appearance of a small amount of blood in the urine, specific therapy was discontinued until February 1st, when 0.3 gm. of arsphenamine was given intravenously. By this time the improvement was striking. The joint symptoms had entirely disappeared, the joints themselves were entirely normal and the lymph glands were definitely smaller. The patient was discharged from the Hospital on February 2, 1924, and has been receiving continuous treatment in the syphilis clinic of the Out-Patient Department. Her blood Wassermann has become negative, she has had no further joint symptoms and the lymph nodes, while still palpable, are decidedly smaller than on admission.

The lymph gland excised for study showed the following characteristics: "Very little of the capsule of the gland has remained on the specimen but the small bit which is present is infiltrated with many mononuclear cells. The cells composing the germinal centres appear to be somewhat larger than those of a normal gland, many of them having an unusually large amount of cytoplasm. The number of lymphocytes present in the rest of the gland is relatively reduced in comparison with the great number of larger, mononuclear cells which are present throughout, sometimes occurring in clumps and cords, and often lying diffusely among the lymphocytes. These cells have round or somewhat irregular nuclei, which are not as dense as the nuclei of lymphocytes and possess varying amounts of cytoplasm. Occasionally a phagocytized particle is seen within one of these cells; cellular degeneration and phagocytosis are, however, very inconspicuous. The endothelial lining of all the blood vessels and lymph channels is greatly swollen; the hilum of the gland contains much scar tissue, while a slight diffuse scarring is present in some areas of the gland substance."

Comment on Case 1

It is impossible to determine from the history of this patient the duration of the infection, but in all probability the syphilis had been present not longer than four years, if that long. Most striking was the enlargement of the lymph glands, all of which were extremely tender. The knee-joints presented the picture of a subacute arthritis with hydrops and without periarticular thickening or changes in bone or cartilage. The temporomandibular, sternoclavicular, acromioclavicular and left ankle joints were also the seat of a subacute arthritis. When first seen, the possibility of the patient having infectious mononucleosis was entertained because of the marked general lymphadenopathy, slight fever and enlarged spleen. However, the blood picture did not bear out this diagnosis, but revealed an eosinophilia for which no cause could be found. The occurrence of the positive Wassermann and the prompt and marked response to antisyphilitic treatment, as shown by the rapid improvement in the arthritis, the diminution in size of the lymph nodes, and the return to normal of the temperature and blood picture left little doubt as to the etiology of the disease. Whatever doubt may have remained after the

favorable response to antisyphilitic treatment was completely dispelled by the positive inoculation results obtained with both lymph node and joint fluid, as described below. No explanation is offered for the pleural rub which was heard on several occasions.

CASE 2

J. B.—Male. Colored. Age 21. Single. Porter. Service No. 50698.

Admitted.—Johns Hopkins Hospital, January 19, 1924. Discharged, February 23, 1924.

Complaint.— "Pains in joints and swelling of neck."

Family History.—Unimportant.

Past History.—General health excellent. Usual childhood infections. At the age of 13, he had an acute urethritis which disappeared after about two months without complications. About nine months before the onset of the present illness he had an indurated, painless, genital lesion which was followed two months later by a generalized skin rash. He received no treatment for this affection. About seven months before admission he had a second attack of acute urethritis which subsided rapidly under treatment.

Present Illness.—About five months before admission he noted a dull pain in both groins which was soon followed by the appearance of a tender, hard, nodular swelling in the left groin. Shortly afterwards numerous joints became painful and his heels became so tender that walking was difficult. Because of his great discomfort he entered a hospital in another state and was discharged after two weeks, feeling quite well. He received no intravenous injections during his stay at that hospital. Shortly afterwards there was a recurrence of the entire process. In December, 1923, he visited the medical clinic of the J. H. H. Dispensary where he was found to have a general lymph-glandular enlargement and a polyarthritis. Shortly afterwards he noted in the left thorax a pain on deep inspiration which lasted for a few days. His blood Wassermann was negative at this time. In January, 1924, he was examined in the urological clinic of the Dispensary and found to have a low grade chronic urethritis and prostatitis for which appropriate therapy was given. Because of the persistence of the pain in the lymph glands and joints he was admitted to the Hospital on January 19, 1924.

Physical Examination.—On admission, temp. 100° F., pulse 86, respirations 20, B.P. 130/85. He was fairly well nourished and appeared uncomfortable only when he moved about. There was a general glandular enlargement. In the neck there was some oedema of the tissues about the glands, so that rather prominent swellings were formed beneath the jaws. The glands varied in size from 0.2-0.3 cm. to 2.0-3.0 cm. in the long diameter. They were firm, smooth, discrete, decidedly tender, freely movable. There was slight enlargement and injection of the tonsils. The heart was slightly enlarged, the sounds were clear. The peripheral vessel walls were a little thickened for the patient's age. There was no active urethral discharge: the prostate was slightly enlarged and irregular. No prostatic secretion could be obtained for examination. There was a polyarthritis involving the temporomandibular, sternoclavicular, shoulder, elbow, wrist, and ankle joints. They were tender to pressure, painful on active or passive movement, but there was no swelling, redness or localized heat about them. The heels were tender to pressure. The reflexes were normal.

Laboratory Findings on Admission

Blood.—		Differential count	
R.B.C.	4,100,000	P.M.N.	70%
W.B.C.	8,800	P.M.E.	10%
Hb (Sahli)	75%	Lymph.	6%
		L. M. Trans.	14%

No abnormal forms of cells were noted.

Urine.—Negative.

Blood Wassermann.—Complete fixation with all antigens.

Stool.—(Repeated examinations) Entirely negative.

Blood Culture.—Negative.

Phthalein Test.—(Intramuscular injection) 60% output in two hours.

X-Ray Report.—January 22, 1924. (Dr. Pierson):—"Tele: M.L. 9.5 M.R. 4 Chest:—Slight enlargement of the heart, no evidence of glands in the mediastinum. Lungs: Clear. Joints: Infectious arthritis of shoulder; ankle negative."

February 4, 1924. (Dr. Pierson):—"Right ankle: Slight arthritis; no evidence of Neisser infection."

Electrocardiographic Report.—Normal sinus rhythm: no abnormalities.

Clinical Course.—The patient was put to bed and given anodynes but there was no subjective or objective improvement. An epitrochlear gland was excised on January 26, 1924, for histological study and inoculation into rabbits. On the following day, eight days after observation in the Hospital, during which time symptomatic treatment failed to relieve his symptoms, antisyphilitic treatment was begun. An intravenous injection of 0.3 gm. of arsphenamine was given and mercury inunctions and iodides were also started. Following this treatment there was a rapid improvement, and on January 30th it was noted that following the administration of arsphenamine the tenderness and stiffness of the joints disappeared and there was no tenderness on pressure over the heels. On February 11th and 18th, 0.3 and 0.4 gm. of arsphenamine were given intravenously and the improvement continued. By February 16th, twenty days after treatment was begun, he was able to walk about the ward comfortably. The lymph glands were still

palpable, but much reduced in size and without any tenderness.

During the first six days of his stay his temperature (rectal) varied between 99° and 101.2° F. After this it remained between 98.6° and 99.4°. It should be noted that the temperature began to drop before specific therapy was started. Upon numerous examinations the eosinophilia varied from 6-15% and the cells of the large mononuclear-transitional group varied from 5-25%. Following the initiation of specific therapy there were no striking changes in the blood picture. The last examination on February 19, 1924 was as follows:

		Differential Count	
R.B.C.	5,500,000	P. M. N.	64%
W.B.C.	9,500	P. M. E.	6%
Hb (Sahli)	80%	P. M. B.	1%
		Lymph	20%
		L. M. Trans.	9%

He was discharged from the Hospital February 23, 1924 and has been receiving antisyphilitic treatment regularly in the syphilis clinic of the Out-Patient Department. There has been no recrudescence of the joint manifestations and the blood Wassermann reaction has become negative.

The lymph gland excised for study showed the following characteristics: "The architecture of this gland is greatly altered by changes which might well be the result of any chronic infectious process. Nothing indicates definitely that the change is of a syphilitic nature. The capsule is markedly thickened and infiltrated in places by small, mononuclear cells which also distend several small capsular lymphatics; the peripheral sinus contains many similar cells. Near the surface of the gland in several places there are irregularly shaped accumulations of round, oval and spindle-shaped cells, many of which have become disintegrated into granular particles of varying size. Some of these have been phagocytized by large macrophages which are quite numerous throughout the gland. The most striking change present is widespread necrosis, which in some places is confined more or less to definite areas, while elsewhere it has occurred diffusely in the gland substance. Some of these necroses are apparently quite fresh and others are in various stages of healing. Only two germinal centres can be recognized and these are composed of cells larger and paler than those seen normally. The blood vessels are slightly thickened and the endothelium of both blood vessels and lymph channels is greatly swollen, giving the gland a diffusely scarred appearance, though in reality very little scarring has occurred except at the hilum, which is quite fibrous."

Comment on Case 2

The clinical picture presented by this patient was similar in every respect to that exhibited by the former, except that there was no splenic enlargement and no hydrops of the knee. The response to antisyphilitic treatment was striking. The possibility that the arthritis was due to gonococcal infection must be discussed. The patient had had an acute urethritis two months prior to the onset of symptoms. He received treatment for this condition and the acute manifestations had entirely subsided before the appearance of the joint symptoms. There was no acute gonococcal inflammation of the genito-urinary tract at the time of admission and treatment for chronic urethritis had not affected the joint symptoms. The duration of the syphilitic infection was probably nine months. The occurrence of a negative Wassermann reaction before admission to the Hospital it is impossible to explain. All subsequent Wassermann reactions were positive until after the patient had received several doses of arsphenamine.

Inoculation Experiments

Case 1.—Inoculations into rabbits were carried out with an excised inguinal lymph node and with fluid aspirated from the right knee. Two rabbits were inoculated with an emulsion prepared by grinding up an inguinal lymph node with sterile salt solution. Each rabbit received 0.3 c.c. of emulsion in the right testicle on January 11, 1924. Orchitis was manifest in each inoculated testicle twenty-five days and thirty-four days, respectively, after inoculation, and aspiration of fluid from each infected testicle showed many characteristic very actively motile specimens of T. pallidum. In one of the animals a scrotal chancre appeared forty days after inoculation.

The joint fluid, which was obtained on the same day that the lymph node was excised, was inoculated as soon as possible after removal from the joint cavity and before clotting had taken place. Dark field examination of the uncentrifuged fluid was negative. Two rabbits were inoculated intratesticularly, each testicle receiving 1.0 c.c. of the fluid. In all four testicles an orchitis developed, the incubation period being thirty-nine days and forty-one days, respectively. In each lesion numerous characteristic actively motile specimens of T. pallidum could be demonstrated.

Case 2.—In this case inoculations into rabbits were made with an emulsion of an epitrochlear lymph node excised on January 26, 1924. The node was ground up in sterile salt solution and the right testicle of each rabbit was injected with the resulting emulsion. Orchitis was evident in each inoculated testicle thirty-one days and thirty-four days, respectively, after inoculation. Characteristic actively motile treponemes were demonstrated in each testicular lesion. No joint fluid was available for inoculation.

Comment

From the foregoing it is apparent that in each inoculated testicle there developed a syphilitic orchitis. This high percentage of positive inoculation results (100%)

would indicate that these two strains possess a high degree of virulence for the rabbit. The subsequent course of the lesions would support this view, although we are not prepared as yet to make positive statements on this point, inasmuch as the study of these strains has only begun. However, they compare very favorably in virulence with other strains which we have recovered recently from patients with early syphilis.

DISCUSSION

These cases have been reported because we are not aware that the particular group of symptoms that they presented, namely, enlarged, tender lymph nodes, eosinophilia and subacute polyarthritis, have been described hitherto as occurring simultaneously in association with syphilitic infection. While, of course, general lymph gland enlargement is common enough in syphilis, the occurrence of marked tenderness of the lymph nodes, such as these patients exhibited, is not common. Eosinophilia has been reported in association with early syphilis and has been regarded by some as in some way linked with the involvement of the skin rather than due to the syphilis itself, although this has been disputed by others.[1] Neither of our patients showed any cutaneous manifestations. The occurrence of a subacute polyarthritis in early syphilis has long been known. In these patients there was no evidence of an acute gonococcal infection anywhere in the genito-urinary tract; on the other hand, the positive inoculation tests with the lymph nodes proved the presence of an active syphilitic infection. In view of the involvement of the temporomandibular and sternoclavicular joints, there was a similarity in the distribution to gonococcal arthritis, and the resemblance was the more striking in the one case with "painful heels." However, the prompt response to arsphenamine treatment leaves no doubt in our minds that the arthritis was syphilitic in nature.

The recovery of *T. pallidum* from the synovial fluid of one of these patients indicates that in syphilitic arthritis these organisms may be actually free within the joint cavity itself. So far as can be ascertained from a survey of the literature, this organism has not previously been recovered from the joint fluid of patients with acquired syphilis. Bertarelli[2] by staining methods demonstrated T. pallidum in the tissues (periosteum, bone-marrow, especially at the line of ossification) in three syphilitic fetuses showing osteochondritis. The fact that the organisms may be found in the joint fluid itself renders unnecessary the assumption of a hypothetical circulating syphilitic toxin to account for the presence of arthritis in patients with syphilis.

CONCLUSIONS

1. The presence of syphilitic infection in the human being may result in a reaction expressed by the following clinical syndrome: (a) enlarged, tender lymph nodes, (b) eosinophilia, (c) subacute polyarthritis.

2. The treponema pallidum may be recovered from the joint fluid of patients presenting the foregoing reaction to the infection.

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PROBLEMS OF TONGUE INNERVATION: COURSE OF PROPRIOCEPTIVE NERVE FIBERS, AUTONOMIC INNERVATION OF SKELETAL MUSCULATURE

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The tongue is innervated by four cranial nerves, the Nn. trigeminus, facialis, glossopharyngeus and hypoglossus. These nerves contain sensory fibers of general cutaneous, gustatory and proprioceptive function and motor fibers to the intrinsic musculature and blood vessels. The fact that the four nerves have, in general, different physiological functions is of enormous interest experimentally, in that it is possible to isolate, imperfectly at least, a group of fibers for study in a manner not possible in many other parts of the body. In regions having more than a single innervation, certain neuro-physiological principles applicable to the entire peripheral nervous system may be advantageously studied. Thus, lingual experiments may be cited having a bearing upon the question of autonomic innervation of skeletal musculature.

THE N. HYPOGLOSSUS

The N. hypoglossus has long been considered the motor nerve to the tongue. Recently it has been shown that it also carries proprioceptive impulses from the intrinsic musculature (Langworthy).[9] Neuromuscular spindles are fairly commonly found in preparations stained with the vital methylene-blue technique. The trunk through which these proprioceptive fibers run was determined by cutting the nerves to the tongue and studying the effect upon delicate movements, also morphological changes in

the spindles after time had been allowed for degeneration to occur. After cutting the Nn. lingualis and glossopharyngeus bilaterally no impairment of tongue function could be observed; the cats lapped milk as well as ever. Nor could any change in the sensory endings be observed when they were stained two or three weeks after the operation. It was not possible to confirm Olmstead's [12] observation that cutting the chorda tympani in the dog caused some paralysis of the tongue on the same side so that the edge could not be curled up as a cup, causing difficulty in drinking.

Cutting the N. hypoglossus bilaterally caused complete paralysis of the tongue. For a day or two after the operation the organ protruded from the mouth but later was withdrawn into it. The cats no longer received adequate nourishment and in most cases it was necessary to resort to tube feeding. They lost weight and their fur became matted and unkept. The mouth became foul and saliva dripped from the corners. After fourteen to eighteen days the animals were killed and the tongue stained with methylene blue. The neuromuscular spindles had almost completely degenerated. It was therefore concluded that the proprioceptive fibers run in the hypoglossal nerve. An endeavor was then made to find the cells giving rise to these fibers.

The N. hypoglossus is now generally considered to be derived phylogenetically from a fusion of three or four segmental nerves which in the course of development have been enclosed in the cranium (Streeter).[21] Originally the nerve segments belonged to the trunk and possessed in addition to the ventral roots both dorsal roots and posterior root ganglia. The sensory roots have become subsequently greatly reduced but a posterior root ganglion is still occasionally found upon the hypoglossal nerve of vertebrates. Thus it was found almost constantly present in the cat. Three ganglia were found upon one nerve in the pig. Froriep [7] described the ganglion in the human fetus and it is often called by his name. It is very rare in adult man.

A typical hypoglossal ganglion of the cat was fixed, sectioned and stained with toluidin blue for histological study. The cells found in the ganglion conform closely in morphological type with those found in the posterior root ganglia of the spinal nerves. The Nissl substance stains as fine dust-like particles scattered rather diffusely throughout the cytoplasm. The cells varied enormously as to size, large cells being freely interspersed with others not half their size.

It was found that cutting the N. hypoglossus caused obvious degenerative changes in the ganglion. A decrease in size of the cells was observed; the nucleus became eccentrically placed and the Nissl substance was clumped and greatly reduced in amount. There were more conspicuous changes in the large cells than in those of smaller size. Sensory cells found in Froriep's ganglion, therefore, give rise to peripheral fibers running in the hypoglossal nerve. Probably all these sensory fibers and cells have a proprioceptive function.

The great variation in the size of the cells in the hypoglossal ganglia may perhaps be correlated with the presence of both medullated and non-medullated fibers in the neuromuscular spindle. The medullated fibers approach the ending almost at right angles to its long axis, piercing the sheath near its center. After entering the capsule they arborize upon the muscle fibers in plaques of the well described spiral or flower-spray design. The non-medullated fibers approach the spindle near its tapering ends. There they end upon the muscle fibers in a group of dust-like plaques. It may be that the large cells in the ganglia give rise to the medullated, the small to the non-medullated fibers.

The hypoglossal ganglia of the cat, even when present, are very small and presumably incapable of innervating all the neuromuscular spindles. Moreover, in many animals and in adult man the ganglia are very seldom found. For this reason it was necessary to look for the sensory cells in other parts of the nervous system. It seemed possible that cells giving rise to primary sensory neurones might, in the course of development, have been included in the medulla in the region of the hypoglossal nucleus. Accordingly, serial sections were made of a cat's medulla in which the hypoglossal nerve on the right side had been cut sixteen days previously. The motor hypoglossal nucleus on the injured side showed obvious changes of degeneration; no trace of any injured cells of the sensory type could, however, be found.

The author has recently made a search for proprioceptive cells included in the neighboring peripheral ganglia. An observation of Sherrington's [17] gives a clue to their possible position. He reported the study of an amyelous human fetus in which the pathological process had destroyed the brain and spinal cord after the neural crests had already formed. The neural crests were not injured and the peripheral sensory neurones and posterior root ganglia were quite normally developed. The N. hypoglossus was present in the fetus and all the branches to the tongue could be identified as well as the N. descendens. When the nerve was traced toward the medulla one group of fibers could be followed to the second cervical ganglion. Another strand joined the vagus just below the ganglia, while a third root ran posteriorly along the dura and there was lost. On the basis of these observations the N. hypoglossus in man, therefore, may be considered to receive afferent fibers from the second cervical and from the vagus nerves.

Additional evidence for the cervical origin of proprioceptive fibers to the tongue was given by van der Sprenkel.[20] He was able to trace the fibers of the N. hypoglossus in cross sections of an embryo of Erinaceus europaeus from the brain-stem to the individual muscles,

which they innervate. Groups of cells in the motor nucleus were identified as innervating separate tongue muscles. He followed sensory fibers from the second cervical ganglion through the hypoglossal nerve to the intrinsic musculature of the tongue.

The evidence of Sherrington and van der Sprenkel was recently confirmed in this laboratory by the following experiment. The upper four cervical ganglia were removed from a cat whose right hypoglossal nerve had been avulsed two weeks previously. They were cut in series and stained with toluidin blue, the ganglia of the normal side being used as controls. The cells in the first, third and fourth ganglia of both sides appeared to be normal. A distinct degenerative change was noted, however, in a number of cells in the right second cervical ganglion. The number of large cells that appeared injured seemed somewhat greater than the number of small cells. The vagus ganglia were examined in the same animal. A small number of cells upon the injured side appeared to be degenerating.

The effect of cutting the sensory fibers from the cervical region upon delicate tongue movements was next investigated. Unfortunately, it was not feasible at the same time to put the fibers reaching the tongue from the vagus out of function. After the cat was anesthetized a laminectomy was performed in the cervical region and the posterior roots of the upper three cervical nerves were isolated and cut at the point where they enter the spinal cord, proximal to the ganglia. Excessive bleeding made the operation difficult but it was finally successfully completed in two animals. They recovered well from the operation and lived till killed after several weeks. Movements of the hind legs were, in both cases somewhat ataxic, probably as a result of pressure upon the posterior columns during the operation. There was at no time any paralysis or ataxia of the tongue, and the cats were able to lap milk as well as ever. Post-mortem examination showed all the posterior roots of the upper three cervical nerves cut in one animal; in the other only a few rootlets of one of the first cervical nerves remained.

An experiment was planned to determine whether strong stimulation of the afferent hypoglossal fibers with an electric current would evoke any pain reactions in the experimental animal. An adult cat was anesthetized, an opening made in the left calvarium and the cerebral hemispheres and basal ganglia removed. Respiration continued normally and the extreme rigidity and immobility commonly seen after decerebration developed. As the preparation had been deprived of sensation by this procedure the anesthetic was discontinued. Then stimulation over the Gasserian ganglion caused the violent reaction that Sherrington and Woodworth [10] described after the application of nocuous stimuli to sensory nerves in these preparations in which the pain centers had been removed. Stimulation of the hypoglossal nerve even with strong current, on the other hand, produced no reaction. It was therefore concluded that no pain fibers ran in the hypoglossal nerve and that maximal stimulation of the proprioceptive fibers gave rise to no painful sensation.

After section of the N. hypoglossus a group of small motor cells of the autonomic type lying ventral and toward the cephalic end of the main motor nucleus are seen to undergo degeneration. The functional importance of Roller's nucleus is as yet undetermined. Van der Sprenkel traced fibers from these cells to the nerve and thought them vasodilator fibers. He believed that some of them might also end upon the striated muscle (accessory motor endings of Boeke). Van Rijnberk considered that they might have to do with the inhibition of tone in the tongue muscle. Molhant called this group of cells N. sublingualis sympatheticus.

In addition, the hypoglossal receives a group or thoracic autonomic fibers from the superior cervical ganglion. It is well established that these are vasoconstrictor fibers to the arteries of the tongue.

A study of many preparations has revealed no decussation of the secondary motor neurones of the twelfth nerve in the medulla. Nor is there any overlap of motor innervation in the tongue. The nerve fibers never cross the midline, and after experimental avulsion of the nerve marked atrophy of the musculature is noted, stopping abruptly at the midline.

Pieces of the N. hypoglossus were stained by the pyridine-silver technique. The axones then appear black, while the myelin sheath may be recognized as a white unstained area around the axone. The nerve was seen to contain a few large medullated fibers, many of medium medullation, and a few small medullated and non-medullated fibers. The somatic motor and proprioceptive fibers probably are covered with a fairly heavy myelin sheath; the autonomic fibers, on the other hand, are non-medullated.

In summary, then, the N. hypoglossus contains somatic motor, proprioceptive and vasoconstrictor fibers, also fibers from Roller's nucleus of unknown function.

N. LINGUALIS

The N. lingualis carries fibers to the tongue derived from the N. facialis through the chorda tympani and fibers direct from the mandibular branch of the N. trigeminus. The trigeminal mediates general cutaneous sensation.

Cushing's [6] observation that the chorda tympani, on the other hand, is the nerve of taste to the anterior portion of the tongue is now generally accepted. Olmstead [11] found that after cutting this nerve the taste buds degenerated over from one-half to four-fifths of the anterior portion. Bulbar autonomic fibers of probable vasodilator function also run in the chorda tympani. Stimu-

lation of the nerve causes an enormous increase in the vascularity of the organ.

Boeke [2] described a third group of non-medullated fibers running through the chorda tympani. They coursed down into the musculature and terminated in dust-like endings upon the striated muscle fibers. This discovery is of great interest, because apparently the intrinsic muscles receive motor fibers from two cranial nerves, somatic motor fibers from the N. hypoglossus and autonomic fibers from the N. facialis.

An attempt was made in this laboratory to isolate the chorda tympani fibers histologically after cutting the hypoglossal nerves and allowing them to degenerate. White rats were used as experimental animals because they are very resistant to infection. The operations were performed without particular attention to aseptic technique. After the animal was etherized the neck was shaved and painted with picric acid. An incision was made in the midline and both hypoglossal nerves were located, all their branches isolated and the nerves then avulsed. While several of the animals died of infection or starvation, a number lived for a fortnight. At the end of two weeks they were killed and the whole body stained with methylene blue. The tongue was then removed and cut into thin slices so that the stain might oxidize.

At this time there had been almost complete degeneration of the hypoglossal fibers and nerve endings so that they were no longer a confusing element in the picture. The bulk of the intact nerve fibers were found upon the cutaneous surface of the tongue, taste fibers and fibers of cutaneous sensation. Non-medullated fibers were also present in the arterial wall, bulbar autonomics with vasomotor function. The arterial fibers were not so plentiful as when the hypoglossal with its vasoconstrictor fibers was intact.

Often fibers were noted which separated from the arterial net or dipped down from the cutaneous group to enter the musculature. There they ended in fine dust-like nerve endings upon the sarcolemma of the muscle fiber. The nerve endings were frequently very long, extending for some little distance along the longitudinal axis of the muscle strand. They may be classified in two groups on the basis of their location in relation to the somatic endings. Many of them terminated at a place upon the muscle where there was evidence of a fragmented somatic motor endplate. Others ended in long arborizations upon fibers showing no trace of a somatic ending. These later muscle fibers appeared smaller than the other muscle strands.

Cross sections of the N. lingualis stained with pyridine-silver were examined. The nerve contains fibers with myelin sheaths and great numbers of unmyelinated fibers. By far the greater number of fibers derived from the chorda tympani are non-medullated.

In summary, the N. trigeminus mediates cutaneous sensation to the skin of the tongue. The chorda tympani, a branch of the N. facialis, carries taste, vasodilator fibers and non-medullated fibers ending upon the striated musculature.

N. Glosso-pharyngeus

The N. glossopharyngeus mediates taste and cutaneous sensation to the posterior portion of the tongue. In addition it is supposed to supply vasodilator fibers to the arteries of the same region. The nerve is made up of a few myelinated and many unmyelinated fibers.

Vulpian's Phenomenon

Physiologists have long searched for evidence to prove or disprove the theory that tone in striated musculature is maintained to some degree at least by autonomic nerve fibers.

Certain invertebrates have muscles whose sole function is the maintenance of postural tone. In Echinus each spine is provided with one muscle which produces movement of the spine, and with another muscle which preserves the posture into which the spine has been brought by its movement muscle. Similarly, bivalved molluscs have striped muscle which, when they contract, produce closure of the shell, and unstriped muscles which retain the shell at any degree of closure, complete or incomplete, to which the former muscle has moved it (Sherrington).[18] Although no example of this differentiation has been found in vertebrates, there are certain experiments pointing toward an autonomic tonic control of striped vertebrate musculature.

An early experiment of Sherrington's [17] has a bearing upon this question. He cut the ventral roots of the nerves to the posterior limb of a cat and the dorsal roots proximal to the ganglia. After time had been allowed for degeneration, the sciatic nerve was exposed and stimulated. This resulted in a slight slow contraction of the musculature. Sherrington found it tempting to hypothesize that this phenomenon was due to the contraction of the intrafusal fibers of the neuromuscular spindles.

Other physiological experiments upon the autonomic innervation of the limb musculature have been reported by Boeke,[2] der Boer [5] and others. Although they have been able to show a slight decrease in tone of the muscle of the limb after section of the autonomic nerve trunk, they have found it difficult to demonstrate an increase in tone upon stimulation of the autonomic fibers.

Van Rijnberk [13,14] has carefully restudied a phenomenon of lingual innervation first described by Vulpian in 1862.[22] Vulpian, investigating the results of anastomosis between motor and sensory nerves, found that if the hypoglossal nerve was cut on one side and the fibers allowed time to degenerate, subsequent strong bipolar

stimulation of the lingual nerve on the same side would cause a slow contraction of the ipsilateral tongue musculature. After the chorda tympani was cut and had degenerated, the lingual nerve no longer gave this reaction. Therefore, the fibers concerned must reach the tongue through the chorda tympani (Vulpian and Philippeaux).[23] Vulpian advanced two hypotheses to explain this reaction. The first that, after the hypoglossal has been cut, the lingual nerve assumes a new function, seems inadmissible. The second, that the excessive vasodilation of the organ after lingual stimulation causes an erection of the tongue simulating contraction, deserves more consideration.

Von Anrep and Czybulski [1] recognized with the plethsmograph increase in the volume of the tongue after stimulation of the chorda tympani even when the hypoglossal nerve was intact. Heidenhain, in 1883,[8] used this fact as evidence that the "pseudo-contraction" of the tongue was a true erection. He further found that injection of defibrinated blood into the carotid under pressure after tying all but the lingual branches caused a raising of the tongue similar to that seen in the experiment. Moreover, injection of nicotine in doses which had no other motor effect upon the tongue produced beautiful movements of the paralyzed side possibly due to the vasodilator reaction of nicotine.

A number of contrary arguments were cited by Van Rijnberk. As the action of nicotine is contrabalanced by curare in doses which are not sufficient to cause paralysis of the arteries, movement of the tongue after application of nicotine cannot be attributed to its vasodilator power. Pinching off the lingual artery was found not to suppress the phenomena. Cyon [4] observed the movement in an isolated tongue.

Neither section of the cervical autonomic trunk nor removal of the superior cervical ganglion without cutting the N. hypoglossus is followed by the contraction of the tongue after stimulation of the N. lingualis. As the vasoconstrictor fibers to the tongue lie in the hypoglossal coming through the thoracic autonomics, according to unanimous opinion, degeneration of the vasoconstrictor fibers ought in itself to be sufficient to produce erection of the tongue.

Van Rijnberk found that section of the hypoglossal nerve inside the skull before the vasoconstrictor fibers have joined the hypoglossal has the same value in producing the phenomenon as section more peripherally. Unless the twelfth nerve carries numerous vasoconstrictor fibers from the medulla, this would prove that the phenomenon does not mean strong vascular dilatation due to suppression of vascular tonus. Moreover, stimulation of the glossopharyngeal nerve, the dilator of blood vessels at the base of the tongue, does not produce, after degeneration of the hypoglossal, any movements of the tongue even when the lingual nerve responds well.

However, it seemed to Van Rijnberk that pressure of the blood had something to do with the phenomenon for a number of reasons. In dogs narcotized with huge doses of morphine (4mg. per kilo) and in whom the blood pressure was low, the reaction was much less intense. After ligating both carotids, which does not entirely cut off the circulation in the lingual arteries (collateral circulation through the circle of Willis), the lingual phenomenon does not entirely disappear but is of feeble intensity. Moreover, when the animal is exsanguinated, the contraction decreases notably, to disappear completely at the end, although the intact hypoglossal remains irritable for a long time. It may be that the blood pressure enters as a mechanical factor. The contractions of degenerating muscle require a great deal of oxygen so that with the diminution of the blood the lingual phenomenon could not be produced.

Heidenhain eventually suggested that excitation of the lingual nerve causes an enormous lymph secretion into the tongue, stimulating the muscle fibers in part degenerated and particularly the terminal plaques which he observed were still quite intact. There is no evidence in favor of this hypothesis.

Van Rijnberk, in the paper already quoted, gave another possible explanation. The vasodilator fibers run through the muscle mass and it might be that the action current in these fibers would stimulate the contraction of the paralyzed fibers in an hyperexcitable condition. Against this view he advanced two arguments. Excitation of the glossopharyngeal nerve produces no movement in the tongue. If the hypoglossal is cut proximal to the entrance of the thoracic autonomic fibers, stimulation of these fibers produces no lingual movement.

All these theories rest on the assumption that the lingual nerve has no direct connection with the tongue musculature and are for this reason incomplete. For Boeke, in 1913, found the accessory nerve endings from the chorda tympani ending on muscle fibers whose motor plaques had degenerated. Van Rijnberk was quick to see the application of this discovery and attributed to these nerve fibers the production of the lingual phenomenon.

Van Rijnberk summarized the salient features of Vulpian's phenomenon as follows: The current required to produce the contraction is much stronger than that required for stimulation of an intact hypoglossal nerve. The latent period is much longer and the contraction slower but longer sustained. As long as the hypoglossal is stimulated the tongue remains in tetany, but when the lingual is stimulated continuous undulating waves of contraction are observed; the tongue is much less set under lingual stimulation. Finally, graphic records after stimulation of the hypoglossal show a short latent period, rapid contraction, tetanic plateau, rapid relaxation after the stimulus is removed. After stimulation of the lingual nerve with much stronger current there is a

much longer latent period, slow contraction, wavy plateau and slow relaxation.

The present author in his study of lingual innervation repeated Vulpian's experiment, and attempted to analyze the tongue movements after degeneration of the twelfth nerves. Former investigators apparently cut the N. hypoglossus unilaterally and studied the effect of stimulation of the N. lingualis on the same side. Although there appears to be no hypoglossal overlap across the midline, it seemed worth while to repeat the experiment after both hypoglossal nerves had degenerated as well as after degeneration of one hypoglossal. The effect of three drugs, pilocarpine, atropine and adrenalin upon the development of the reaction was observed.

Vulpian's phenomenon was observed in seventeen experiments upon cats. Two typical protocols from this group are given:

Exp. No. 14.—Adult cat, male, well nourished.

Sept. 25, '23.—Ether. Neck shaved and animal prepared for sterile operation. Incision made in the midline of the neck and both hypoglossal nerves exposed just above the thyroid cartilage. All the branches were isolated, the nerves traced to a point posterior to the common carotid artery and avulsed.

Sept. 26.—The tongue protrudes somewhat from the mouth.

Sept. 27.—Cat active. No infection of the wound. The tongue has been withdrawn into the oral cavity. Attempts to drink milk by placing the whole mouth in the dish and sucking the fluid. No voluntary movements of the tongue can be observed.

Oct. 5.—Animal has lost considerable weight and appears ragged and unkept; wound healing satisfactorily. Tube feeding instituted.

Oct. 13.—Seventeen days after primary operation. Cat emaciated and weak. Has been tube-fed twice a day since Oct. fifth. Wound healed. Preparations made for conclusion of experiment.

2.00 P. M.—Ether. Insertion of tracheal tube for administration of anesthetic. Neck shaved. Nn. lingualis and glossopharyngeus exposed bilaterally. Region of peripheral ends of cut Nn. hypoglossi also uncovered. Gag placed in mouth and tongue held in view by string through tip.

There is some atrophy of the tongue musculature. Fibrillary contractions are easily visible upon the under surface. The blood vessels stand out plainly beneath the skin and the finer arteries along the edge of the tongue appear dilated. No voluntary movements of the muscle occur.

2.45 P. M.—Stimulation of the region of the peripheral ends of the cut hypoglossal nerves with a current of moderate or even greater intensity causes no contraction of the lingual musculature. Likewise, stimulation of the glossopharyngeal nerves is without apparent effect.

Stimulation of the lingual nerves with moderately strong current causes movements of the tongue upon the ipsilateral side analyzable under three distinct heads. There is great increase in the fibrillary contraction of the musculature. Secondly, upon the application of the electrode, a slow undulating wave of contraction may be followed along the edge of the tongue. This contraction is very definite and may be observed whenever the stimulus is applied. Thirdly, after a definite latent period, great vasodilation may be noted with decrease in the antero-posterior axis and great thickening of the tongue. The tongue is slowly lifted from the roof of the mouth where it has been lying, only gradually to fall back again after removal of the stimulus. This last phenomenon appears to be an erection due to the great inflow of blood.

3.10 P. M.—Injection of 0.5 c.c. adrenalin hydrochloride. Immediate stimulation of the nerves. The drug apparently has no effect upon the results already described.

3.25 P. M.—Subcutaneous injections 0.1 gr. pilocarpine hydrochloride.

3.45 P. M.—Animal markedly salivated. Great vasodilation of the blood vessels of the tongue. Contraction of the musculature upon stimulation of the lingual nerve appears much less active than before

4.20 P. M.—Preparation still in excellent condition. Movements of tongue upon stimulation of lingual nerves less active than at the beginning of the experiment.

Animal killed. Specimens preserved for histological study.

Exp. No. 9.—Sleek adult cat, female.

Oct. 12, '23—Ether. Neck shaved and incision made in the midline with sterile precautions. Hypoglossal nerve on right side exposed, isolated and avulsed.

Oct. 13.—Cat in good condition. Tongue, when protruded, deviates markedly toward injured side.

Oct. 17.—Wound healing well. Animal eats with some little difficulty.

Oct. 30.—Eighteen days after primary operation. Cat well nourished, wound healed. Preparations made for the final experiment.

2.00 P. M.—Ether. Insertion of tracheal tube for administration of anesthetic. Nn. glossopharyngei, linguales, intact N. hypoglossus and peripheral region of avulsed nerve exposed. Gag placed in mouth and tongue held in view by thread through its tip.

The tongue, when voluntarily protruded, deviates toward the injured side. There is distinct atrophy of the musculature upon the right or injured side, and fibrillary contractions are easily seen. The blood vessels stand out with great clearness and the arterioles near the edge of the tongue appear more dilated than on the normal side.

2.45 P. M.—Stimulation of the intact twelfth nerve with weak current causes contraction of the ipsilateral tongue musculature with further deviation of the organ toward the injured side. Stimulation of the region of the peripheral end of the cut hypoglossal even with strong current elicited no movement of the tongue. Similarly, stimulation of both glossopharyngeal nerves gives no apparent reaction. Stimulation of the lingual nerve on the intact side is without effect.

On the other hand, stimulation of the N. lingualis on the injured side with moderately strong current produces obvious ipsilateral tongue movements. After a brief latent period definite waves of contraction pass along the injured edge of the tongue. The fibrillary contractions increase until the skin on the under surface becomes wrinkled and puckered. Finally, the vascularity increases tremendously till the organ appears swollen and is lifted from the roof of the mouth where it has been lying.

3.05.—Injection 1/150 gr. atropine sulphate.

3.25.—Stimulation of the lingual nerve upon the right side gives results similar to those previously recorded.

3.45.—Animal still in excellent condition. There is no apparent increase or decrease in the movement of the injured side of the tongue after stimulation of the lingual nerve. Cat killed.

Discussion

The lingual phenomenon of Vulpian may be demonstrated as well after degeneration of both hypoglossal nerve as when one nerve is intact. This rules out the possibility that stimulation of overlapping hypoglossal fibers is responsible for the reaction.

It is possible to analyze the tongue movements occurring upon stimulation of the lingual nerves after the hypoglossals have been cut and have degenerated, under three distinct headings. A great increase in the fibrillary contraction of the muscle is seen. It is probable that the action current running through the lingual nerve fibers stimulates directly the hyperirritable degenerating musculature. There occurs also a great vasodilation of the tongue, causing it to swell and bulge, and finally to be raised from the roof of the mouth in a manner simulating a true contraction. This erection of the tongue has been given particular attention by earlier investigators. But, in addition, there appears after stimulation of the lingual a slow wavy contraction of the musculature, poorly sustained, with a long latent period and continuing for an appreciable time after removal of the stimulus. The author has no new explanation for this contraction. It seems tempting to believe, however, that it is due to stimulation of Boeke's accessory nerve endings.

The case would be stronger for considering this as a demonstration of autonomic tonic innervation of skeletal muscles if the accessory fibers were of thoracic autonomic origin. They appear, on the other hand, to belong to the group of bulbar autonomics. However, pilocarpine in suitable doses, a drug which in general stimulates the bulbo-sacral group of fibers, appears to cause the reaction to decrease and disappear rather than increasing it as one might expect. Atropine and adrenalin, on the other hand, seem to have no effect upon it whatsoever. Possibly, we know too little about the minute action of these drugs at the present time to enable us to draw any definite conclusion from them. A search for the cells of origin of the autonomic fibers must eventually be made.

Two other phenomena of the same kind remain to be mentioned. Naito [10] reported that while the phrenic nerve supplied somatic motor fibers to the diaphragmatic musculature, the tone of the muscle was maintained by autonomic nerve fibers reaching the muscle through the phrenic plexus. Tone remained after cutting the phrenic but disappeared after painting the coeliac ganglion with nicotine. Van Rijnberk was not able to repeat the results of Naito. Schlaepfer [16] demonstrated that after cutting the phrenic nerve in the dog there was complete degeneration of the ipsilateral diaphragmatic musculature.

The third example has to do with the innervation of the upper lip. Rogowicz [15] found that after the facial nerve had been cut and allowed to degenerate, stimulation of the Ansa of Vieussens caused a contraction of the upper lip. This experiment was repeated by Van Rijnberk with affirmative results and seems of all three experiments the most conclusive, since here there is the possibility of tonic innervation through the thoracic autonomic group.

SUMMARY

The N. hypoglossus mediates somatic motor fibers to the tongue. Vasoconstrictor fibers from the superior cervical ganglion also join the nerve. In addition, it carries proprioceptive fibers from neuromuscular spindles present in the intrinsic tongue musculature and fibers of unknown function derived from Roller's nucleus in the medulla. A rudimentary sensory ganglion is found upon the N. hypoglossus of many vertebrates. As this ganglion has gradually undergone regression, the sensory cells have become incorporated in the second cervical and in the ganglia of the vagus nerve.

The N. lingualis received fibers from two cranial nerves. The N. trigeminus mediates cutaneous sensation to the tongue. Fibers from the N. facialis, running through the chorda tympani are gustatory and vasomotor in function. In addition, the chorda tympani contains fibers ending in accessory motor plaques upon the striated tongue musculature. The N. glossopharyngeus mediates gustatory, general cutaneous and vasodilator fibers to the posterior portion of the tongue.

After the hypoglossal nerves have been cut and allowed to degenerate, stimulation of the lingual nerves with a strong current causes slow undulating contraction of the musculature. This contraction differs from the normal in the greater strength of current required to elicit it, the long latent period, poorly sustained plateau and slow relaxation. At the same time fibrillation of the degenerating muscle is greatly increased and enormous vasodilation causes almost an erection of the tongue. It is tempting to believe that this contraction is due to stimulation of the accessory motor endings whose fibers are seen in the N. lingualis. If this be true, it illustrates the effect of stimulation of autonomic nerve fibers innervating skeletal musculature.

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SPONTANEOUS PERISTALSIS OF THE EXCISED WHOLE UTERUS AND FALLOPIAN TUBES OF THE SOW WITH REFERENCE TO THE OVULATION CYCLE

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Introduction

In recent years the interesting fact has been established that the spontaneous contractions of the uterus as well as of the Fallopian tube show periodic variations in relation to the ovulation cycle. Blair [1] first reported this phenomenon in a brief note on the uterus of the rat. The spontaneous rhythmical contractions of one horn of an excised rat's uterus, suspended in warm oxygenated Locke's solution, were recorded by means of a lever writing on a kymograph. The rhythm was found to be slowest at the time of oestrus, increasing gradually to a maximum late in the resting stage and decreasing rather suddenly at the pre-oestrus. Working independently on the sow's uterus, Keye [2] also observed cyclic variations in the spontaneous contractions of uterine muscle coincident with the histological changes which take place in the reproductive tract during the oestrous cycle. The method employed consisted in suspending a transverse strip of uterine wall in a bath and recording the contractions of the muscle on a kymograph by means of a lever. He found two types of spontaneous contractions present in the isolated uterine musculature: contractions of relatively great amplitude and of long duration; and superimposed upon these, contractions of relatively lesser amplitude and shorter duration. Coincidently with the growth and rupture of follicles and for a short time afterwards the major contractions predominated. The minor contractions, on the other hand, appeared with the growth of the corpora lutea, continuing to increase in number until about the 13th day after ovulation. From the 14th day they decreased in rate while the major contractions gradually recommenced. By the 20th day the large contractions were almost at their height of activity, while the small contractions were rapidly diminishing in rate with the advent of a new cycle. Keye suggested that these variable contractions which are probably of a peristaltic nature may be the active agency in transporting the ova and early embryos to their final position for implantation in the uterus.

Observations on the variation in activity of the Fallopian tube of the sow and monkey with reference to the ovulation cycle have been made by Seckinger [3] and Seckinger and Corner.[4] Their methods, similar to Blair's and Keye's, consisted in studying the Fallopian tube suspended in warm oxygenated Locke's solution and attached to a lever which recorded on a kymograph. Two definite types of spontaneous contraction of the tube were observed during the oestrous cycle. The first type occurred during oestrus and was marked by the presence of rapid, irregular contractions. These ceased after the follicles had ruptured and the ova had reached the uterus. The second type, occurring during the interoestrous period, was relatively slower and the contrac-

tions were of equal amplitude and rhythm. The change from the inter-oestrous to the oestrous type of contraction took place after the follicles had reached a diameter of 7 to 8 millimeters. The contractions of the tube during early pregnancy were identical with those of the inter-oestrous period. The oestrous type of contraction, provides perhaps, according to Seckinger, a mechanism suitable for the transportation of the ova through the tubes into the uterus. Furthermore, Seckinger suggests the possibility of a secretion of the theca interna responsible for the contractions occurring during oestrus, basing this idea upon the synchronous occurrence of the physiological changes in the muscle contractions and cytological changes observable in the cells of the theca interna of the maturing follicles of 7-8 millimeters.

The interesting observations of these previous investigators which we have briefly described were made on strips or rings of muscle suspended so as to allow graphic records to be made. We proposed to study tubal and uterine contractions in a somewhat different way. Instead of using excised pieces of musculature we decided to observe the freshly excised but otherwise intact internal genital tract of the sow in a bath by means of the naked eye. We hoped in this manner to be able to see spontaneous muscular activity of the tubal and uterine musculature and possibly to distinguish differences in activity during the various periods of the ovulation cycle. To what extent we were successful in this will be outlined in the following pages.

The sow was the animal of choice for several reasons. There was abundant material from this animal which could be readily obtained during slaughter from a nearby abattoir. Secondly, the uteri and tubes were relatively large, hence well adapted to direct observation. Finally, the careful work of Corner[5] upon the oestrous cycle in the sow gave us the necessary information by which specimens could be dated.

The material was got at an abattoir which has Federal meat inspection, and thus we were able to determine and reject the specimens from obviously diseased sows. The entire internal genitalia were obtained intact as soon as the animal's abdomen was cut open (ten minutes after the sow had been killed by sticking). The cervix was cut across at the junction of the middle and distal thirds, and the ligaments were severed close to the body wall, leaving cervix, uterine cornua, tubes, ovaries and broad ligaments in their normal relationships. The uterus and its appendages were immediately placed in a glass dish of cold Locke's solution. The specimens, which on later observation in the laboratory proved most active, contracted vigorously at the slaughter-house when the warm tissue was immersed in the cold bath. The contractions lasted from one half to one minute, then the uteri became quiescent and atonic, only to resume their activity when transferred to warm oxygenated Locke's solution at the laboratory. It was also observed that the material which did not contract in the laboratory rarely, if ever, contracted when placed in the cold bath at the slaughter-house. In the laboratory the uteri were then placed in a bath containing warm well oxygenated Locke's solution, in groups of from three to six specimens. The temperature of this bath was kept as nearly constant (between 37 and 38° C.) as possible. The bath was commodious enough to hold four medium-sized uteri (75-150 gms.) without crowding one another when they were spread out with both uterine cornua, and the tubes and the ovaries in view.

The uteri were observed as a rule for a period of one half-hour, although, in order to ascertain whether longer immersion in the bath would change our results, a number of uteri were watched as long as an hour. We found that the maximal contraction occurred during the first half hour and that longer immersion in the bath resulted only in many of the vigorous uteri going into a state of tonic contraction in which they became refractory.

A method had to be adopted for expressing our results. We found it impracticable to denote the contractility of the uteri in terms of rate of contraction because of the irregularity of the contractions, as shown by briefer or longer periods of quiescence alternating with similar periods of muscular activity. We therefore chose to designate the character of the muscular movement observed over a half-hour period by one of the following terms: as "none," "very feeble," "feeble," "feeble-moderate," "moderate," "moderate-vigorous," "vigorous," or "very vigorous." This method was of course purely subjective. It had, however, the safeguard that two persons were making the observations at the same time. Moreover, we were working on a large number of specimens so that errors in judgment or variations in individual specimens fluctuated about a mean for a given group of uteri. We observed in all 186 uteri of which the last 136 consecutive ones, arranged in groups according to their places in the ovulation cycle, were made the basis for our final conclusions. A further control was that we always observed three to six uteri in the bath at the same time under identical conditions which allowed us to make immediate and direct comparisons of a number of specimens.

We found that it made no difference whether the uteri, immersed in the bath at the same time, were of the same or of different phases of the ovulation cycle. In the many observations made we never noted a reciprocal action of one uterus upon another through the possible mediation of hormones liberated into the bath.

After the uteri had been observed in the bath, and their activity determined, they were taken out and examined. The ovaries were examined with especial reference to the number and size of the follicles, and the presence of corpora lutea of the existing or of previous

ovulation cycles. The dimension and character of the corpora were noted. When recently ruptured follicles or corpora lutea were present, the tubes and uterus were washed out with salt solution for ova or blastocysts. Notes were also made on the presence and character of any fluid found in the uterus, as well as on the character of the uterine mucosa, any abnormalities, etc. In making our observations on the presence of ova or blastocysts we followed the method described by Corner.[5]

Observations

We observed from the very beginning of our experiments that spontaneous contractions of the tubes and uterus can be easily seen with the naked eye. When several uteri were placed in the bath they were at first quiescent, but in a few minutes tubal and uterine movements began. The tubal movements almost invariably started before those of the uterus. It has been observed also, when the specimens were placed in the bath and the temperature gradually raised to 37.5° C., that the tubes commenced to contract at temperatures as low as 32° to 34°, whereas the uterus seldom showed movement at temperatures below 36°.

Character of the contractions.—The chararcter of the movements observed was predominantly peristaltic in nature, although antiperistalsis was now and then seen. The variations in the peristaltic waves, however, necessitate our describing in more detail the different types of peristalsis which we saw.

The movements of the tubes were predominantly peristaltic though antiperistalsis was occasionally observed. The peristaltic waves originated in the upper third of the tube and ended at a variable distance lower down, some of the waves extending no farther than one or two centimeters, others travelling down vigorously as far as the isthmus, while others continued into the uterine cornu. Not infrequently the tube showed several segments swaying peristaltically at the same time. This was the result of fresh peristaltic waves being initiated above before the previous ones had subsided below.

In the uterus different kinds of activity were observed. The waves were predominantly peristaltic, travelling from the cornual end of the uterus toward the cervical portion. Occasionally, a wave started at the tubal uterine junction and passed the whole way down the uterus. More often the waves commenced at the tip of a cornu or in a loop of uterus lower down and travelled for a variable distance down the uterus. Frequently a fresh wave originated in the tip of a uterine horn before the previous one had subsided below. Sometimes peristalsis was initiated independently in several segments of the uterus so that there were three or four areas of uterus moving peristaltically at the same time. This phenomenon gave the uterus a swaying or writhing motion. In a vigorous specimen the peristaltic movements were sufficiently strong to lift whole loops of the uterus off the floor of the bath to a height of from two to three centimeters, or, in the case of the tip of a cornu, to drag the attached tube or ovary violently across the floor of the bath. Now and then antiperistaltic waves, seldom travelling as great a distance as the peristaltic ones, were seen passing up from a lower to a higher segment of the uterus. As a rule, no very definite constriction rings, as are familiarly seen in contracting intestinal musculature, could be made out in association with the peristaltic movements. In several thick-walled uteri, however, which were contracting slowly but forcibly, a moving band of constriction could be seen passing down a relaxed loop of uterus. In very active specimens we noticed at times a purely independent and localized movement of the cervix. In these instances the cervical stump raised itself from the floor of the bath and swayed rhythmically in a dorso-ventral plane before relaxing.

In addition to the above phenomena we have observed another type of activity in uteri, the walls of which were rounded with probably tonic musculature, in contradistinction to others which appeared flat, flaccid and rather toneless. These tonic uteri, besides exhibiting short peristaltic movements, frequently performed a number of vigorous purse-string-like contractions of the whole uterus resulting in a gradual bunching up of the organ into a spherical mass which then showed no further signs of spontaneous muscular activity.

The peristaltic movements which we have described occurred with no definite regularity, so that it has been impossible to compare uteri with one another on the basis of rate of contractions. Some uteri from the beginning showed alternating periods of rest and activity. Others were nearly continuously active in some or every portion of their musculature. Several peristaltic waves which traversed the uterus from tube to cervix took 8 to 12 seconds to accomplish the passage, a distance of about 30 cm.

Peristaltic waves which traversed the lower portion of the uterus ended in the cervix. Never have we observed a peristaltic wave passing down one uterine cornu, to continue around and up the opposite horn as an antiperistaltic contraction.

Both Fallopian tube and uterus reacted to mechanical stimulation such as pinching. A vigorous uterus during quiescence reacted promptly, as a rule, to gentle pinching by undergoing a series of contractions. A sluggish uterus frequently responded by several vigorous contractions on repeated pinching. A completely inactive uterus usually remained refractory even to repeated stimulation. The response to pinching of an active uterus differed from that of the intestine. There was no sign in the uterus of the formation of a constriction ring at the point of stimulation with peristaltic and antiperistaltic waves proceeding from it. In the uterus the place that was pinched

relaxed on removal of the forceps and after a refractory period of variable length (1 to 10 seconds) the uterine muscle in that region initiated several or a series of peristaltic or antiperistaltic movements.

Relation of tubal and uterine movements to the ovulation cycle.—For the purpose of convenience in discussing our results we have divided the ovulation cycle of the sow, which comprises twenty-one days in all, into the following periods. In this table Day 1 represents the day of ovulation.

Period of degenerating corpora	15th to 19th day.
Period of mature follicles	19th to 21st day.
Period of tubal ova	1st to 3rd day.
Period of uterine ova	3rd to 7th day.
Period of large corpora	7th to 15th day.

In addition, observations are presented on tubal and uterine movements during the period of the formation of blastocysts and embryos, as well as upon immature uteri.

Period of degenerating corpora (15th to 19th day).—During the early part of this period the tubal movements are "feeble," but they decrease towards the end of the period to "very feeble." The activity of the uterus throughout this period is "very feeble," reaching for a time total inactivity.

Period of mature follicles (19th to 21st day).—This period which begins with the onset of oestrus and terminates with the rupture of the mature Graafian follicles is characterized by the rapid growth of the follicles from 6 or 7 millimeters to their mature size. A change occurs in the tubal contractions when the follicles reach a diameter of 7 to 8 millimeters from the "feeble" ones of the preceding period. The activity of the tubes increases sharply, at first becoming "moderate," then "vigorous" and, finally, at the time of ovulation becoming "very vigorous." The uterus, on the other hand, shows no change, remaining as inactive as it was at the end of the preceding period.

Period of tubal ova (1st to 3rd day).—This period commences at the time of ovulation and ends at the time the ova leave the tube to enter the uterus. The ovary during this period is characterized by the presence of ruptured follicles (early corpora lutea). The tubal activity which had become "vigorous" or "very vigorous" during the preceding period remains "very vigorous" throughout the period of tubal ova.

The uterus, which was inactive during the period of maturing follicles, at the time of ovulation quite suddenly becomes "very vigorous" in its contractions and maintains this great activity throughout the period during which the ova are in the tubes.

Period of uterine ova (3rd to 7th day).—At the onset of this period the ova have entered the uterus, and by the end of the period, unless they have become fertilized, they are degenerating. Meanwhile, the corpora lutea are developing rapidly, attaining their maximal size by the seventh day. The tubal movements during this time gradually become less active, sinking by the end of this period to "moderate." The uterus during this period also undergoes a gradual decline to "moderate" activity by the end of this phase.

Period of large corpora (7th to 15th day).—About the seventh day the corpora have reached their maximal size and maintain this size until about the fifteenth day, when they begin to regress. During this period both tube and uterus show a further gradual decline in activity from "moderate" to "feeble," or "very feeble," at the close of this period.

We have thus briefly described the tubal and uterine movements in one complete ovulation cycle. The course of events is shown diagrammatically in the appended chart.

Period of blastocysts and embryos.—If the ova become fertilized in the tubes, they segment and, on entering the uterus, develop into blastocysts instead of undergoing degeneration by the seventh day. Finally, after implantation, which occurs near the end of the second week, the embryo begins to form. In such an event the tubal and uterine movements, which by the seventh day have diminished to "feeble" and "moderate," respectively, no longer continue to subside as they would ordinarily in the course of the ovulation cycle, but continue on a constant level of "feeble" and "moderate" activity into the period of gestation as far as we have followed it (12 mm. embryos).

Immature uteri.—We have examined a large number of immature uteri. The results have been quite constant. Both tubes and uterus exhibit "very vigorous" peristaltic movements during this period. We have investigated also the bahavior of the immature uterus when it enters its first oestrus. An analysis of our data leads us to believe that tubes and uterus undergo vigorous peristalsis throughout the first oestrous period both before and after ovulation. It is only in subsequent oestrous cycles that we observe quiescent uterine musculature preceding ovulation.

Our observations have led us to recognize several different types of oestrous uteri. First, there is the oestrous uterus possessing ovaries which contain well-defined corpora lutea of a previous ovulation. The corpora in these are, as a rule, pale yellow, flat or slightly protuberant, and measure from 3 to 5 millimeters in diameter. The follicles measure from 8 to 11 millimeters in diameter. The uterus itself is large, flaccid and lacks muscular tone. These uteri do not contract spontaneously in the bath.

Second, there are uteri which possess ovaries containing large follicles (8-11 mm.) but no corpora lutea. These might be either immature uteri entering the first oestrous cycle or ones that had passed through an ovulation cycle at some previous period with a complete disappearance in the meanwhile of the corpora of the pre-

vious ovulation. These uteri are in appearance identical; they are, as a rule, round and give the impression of possessing muscular tone. This group, however, in our experience permits a further subdivision on the basis of physiological activity into those which contract vigorously in contradistinction to others which do not contract at all. Whether the active uteri of this group which in general weigh less than the inactive ones are immature, whereas the others are mature ones which have ovulated before, cannot be definitely determined, because on microscopic section the end stage of a corpus luteum cannot be differentiated from the scars of atretic follicles.

Discussion

These observations which we have made show that the musculature of the Fallopian tube and of the uterus contracts peristaltically. Further, they show that the direction of the peristaltic waves is predominantly from the fimbriated portion of the tubes towards the uterine horn and from the uterine horn towards the cervix. Antiperistalsis occurs spontaneously in both tubes and uterus, but is relatively more frequent in the uterus.

It is of interest to examine these findings in the light of the theory of gradients in axiate structures. Child [6] hypothesized that the activity of axiate structures, whether entire organisms or only axiate structures in more complex organisms, is controlled by a gradient of metabolism. Examples of such structures are the intestine, heart and the ureter. Such an organ, according to this hypothesis, is normally controlled by the area of highest metabolism. From this dominant area a gradient occurs to areas of lower metabolism. Gradients measured by CO_2 production and catalase have been demonstrated in the intestine by Alvarez [7] and by CO_2 production in nerve fibers by Tashiro.[8] In the latter the gradient is oriented in the direction of the propagation of the nerve impulse.

In tubular organs with a muscular wall there exist gradients of muscular activity associated with the metabolic gradient. For example, Alvarez [7] has shown that the rhythmic contraction of the musculature of the intestine is graded downward from the pylorus to the ileocoecal valve. In the intestine, in addition to these, gradients of irritability and of the latent period have also been demonstrated. Penfield [9] has brought forward considerable evidence to show that there is a gradient of rhythmicity in the ureter. He has established the fact that the musculature of the renal pelvis dominates the activity of the normal ureter, acting as a pacemaker for the peristaltic waves which pass down the ureter.

Evidence has been adduced to explain the occurrence of antiperistalsis to the gradient theory. It has been shown that irritation, trauma, inflammation, poisons and similar causes, acting locally on a muscular tube, can produce an area of heightened metabolism measured in terms of catalase or CO_2 production, associated with a rhythmical gradient of muscular activity extending to regions of lower metabolism. Thus, when a loop of intestine is pinched, a constriction ring forms for a time at the site of stimulation which gives off rhythmical contractions up an down the intestine.

Concerning the rhythmicity and dominant regions of metabolism in the Fallopian tubes and uterus little is known. Alvarez,[7] however, remarks that he has records from segments of Fallopian tubes which suggest strongly that there are rhythmic gradients in those tubes.

Our experiments present considerable evidence of the presence of rhythmic gradients in both Fallopian tubes and uterus. The pace-maker or dominant area for tubal contractions appears to be, as a rule, in the distal third (fimbriated end). From this region the peristaltic waves pass along the tube towards the uterus.

In the uterus a rhythmical gradient appears to exist from the uterine horns towards the cervix. However, our observations on the uterus point to no very strong dominance of any one area or to a very sharp gradient of its musculature, because it is only the occasional peristaltic wave that originates in the tip of the uterine horn and traverses the entire distance to the cervix. More frequently the peristaltic waves arise at points intermediate between the tip of the cornu and the lower portion of the horn to pass for variable distances towards the cervix. Moreover, the not infrequent spontaneous antiperistaltic movements of the uterus point to the presence of a rather unstable gradient. Furthermore, in contrast to other muscular organs, we are dealing in the tubes and uterus with a structure in which the rhythmical gradients are subject to cyclic variations coincident with the other phenomena of the oestrous cycle.

Several observations indicate that the tubal gradient is more stable than the uterine and is more definitely polarized. Antiperistalsis is relatively infrequent in the tube as compared with the uterus. Furthermore, peristalsis commences much sooner in the tubes than in the uterus when the specimens are put into the bath; besides which, the tubes contract in the bath through a much wider range of temperature than the uterus.

In contrast to both intestine and ureters, the tubes and non-gravid uterus, as a rule, contain inconsiderable quantities of fluids or solids and hence internal pressure as a causal factor in stimulating peristalsis is unlikely. The ova can scarcely be considered as producing any adequate mechanical stimulus. We have noticed variable amounts of free fluid at times in the sow's uterus. This fluid which is of a yellowish color occurs in the uterus in greatest abundance during the period of tubal ova. In a series of 18 such specimens we have made a note of the presence of fluid in 8 instances. During the period of large corpora we have seen fluid in 4 out of 28 specimens; during oestrous in 1 out of 14 cases; in immature

specimens in 2 out of 19. The uteri containing fluid were not more active than those from the same phase of the ovulation cycle which contained none. Moreover, in the gravid uterus after implantation has occurred, during the period when the allantois and amnion are filling rapidly with fluid, no augmentation of uterine activity takes place.

Comparing the results of our naked-eye observations on the activity of the tubes and uterus with those of Seckinger and Keye obtained from the study of ring and strip preparations recording on a kymograph, we find considerable agreement and yet notice certain differences. With Seckinger's observations on the tubes our results coincide closely. We have observed the same rather sharp rise in tubal activity during oestrus which reaches a maximum during the period of tubal ova. We had also noticed the subsequent gradual decline of tubal movement during the periods of uterine ova and of large corpora.

Our own observations differ from Keye's in so far as during the first half of oestrus, before ovulation has occurred, we observed practically no uterine activity unless the uteri were immature ones approaching the first oestrous period, in which case the movement of the uterus was vigorous. Keye does not raise the question of the several types of oestrous activity. It would be of interest to extend these observations to suspended ring or strip preparations of the different kinds of oestrous uteri.

Moreover, by our method we have not been able to distinguish the two types of contractions which these observers saw, the oestrous and inter-oestrous types seen in the tube by Seckinger, and the major and minor contractions recorded by Keye in the uterus. From the nature of the two methods it is likely that ours is unadapted for the discernment of the two types of contraction which they describe.

The suggestion of these observers that the tubal and uterine contractions play a rôle in the transportation of the ova through the tubes into the uterus, and possibly in the final spacing of the blastocysts in the uterus before implantation, may possibly receive further substantiation from our observations. The tubal contractions commence before ovulation, hence it is not unlikely that currents are produced in the neighborhood of the ovaries at the time of rupture of the follicles which facilitate access of the ova to the tubes and prevent the ova from becoming abdominal. During the period of tubal ova the tubes are most active. During the period of uterine ova the uterus is moderately active, and it is possible that the peristaltic as well as the antiperistaltic movements, which we have observed in the uterus, materially facilitate the transportation and spacing of ova within the uterine cavity.

The question arises to what extent the behavior of the excised uterus, as we have observed it, compares with that of the uterus actually *in situ* in the living animal. This question affords a whole new avenue of investigation into which we have not entered except to make a few observations on the uterus in the living dog. Three dogs were given paraldehyde, one received ether; whereupon the abdomen was opened and the internal genitalia were inspected. We kept the peritoneal cavity bathed in warm Locke's solution. The tubes could not be observed, but a portion of the uterine cornua and of the cervix could be brought into view with little manipulation. We made the observation that spontaneous peristaltic contractions of the uterus could be clearly distinguished by this method. Our series of dogs was too small, however, to permit any statements upon the movements of the uterus in reference to the dog's ovulation cycle.

SUMMARY

1. The whole internal genitalia of the sow were observed in a bath of warm oxygenated Locke's solution. Spontaneous peristalsis and antiperistalsis were observed in both Fallopian tubes and uterus. The existence of a rhythmic gradient is discussed.

2. The muscular activity of the tubes and uterus show cyclic variations coincident with the ovulation cycle.

3. This activity suggests a possible mechanism for the transportation of ova.

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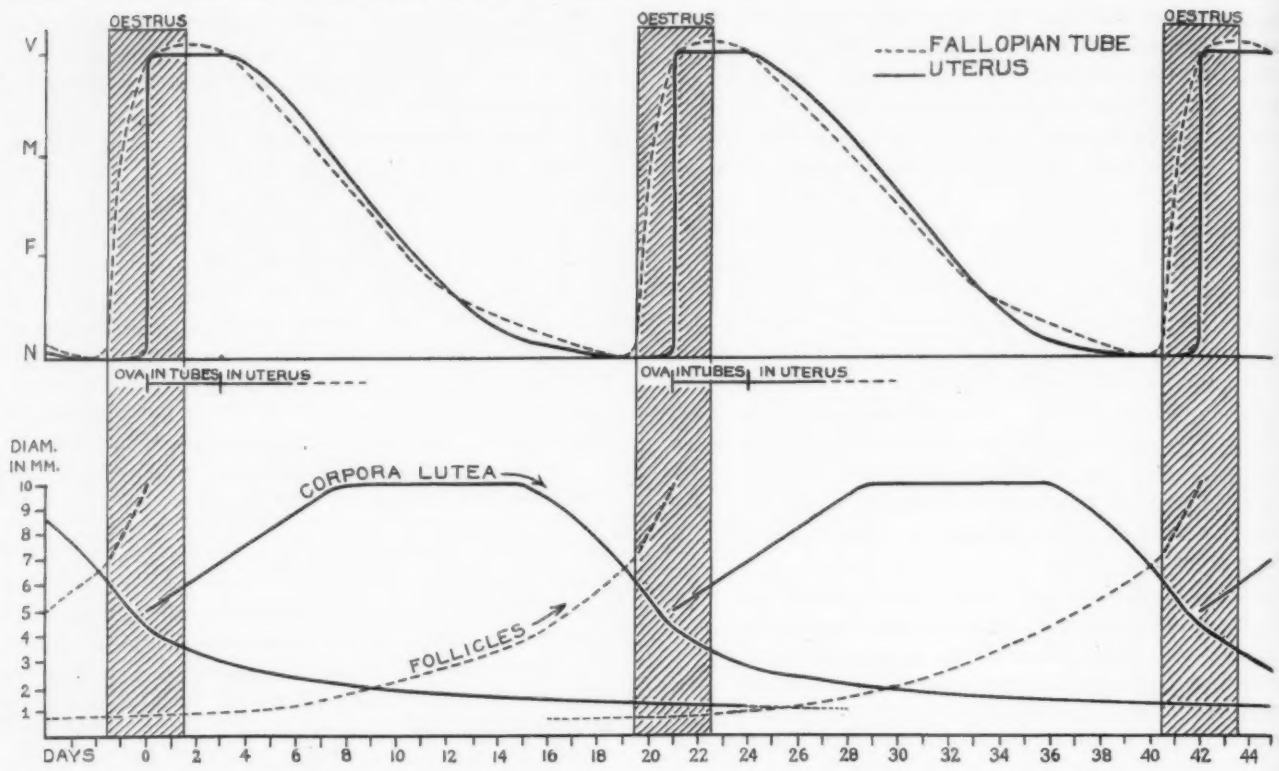

DESCRIPTION OF DIAGRAM

The lower half of the diagram, modified from a graph by G. W. Corner,[2] shows the relations between oestrus, ovulation, and the growth and retrogression of the corpora lutea during the ovulation cycle of the sow. The upper half of the diagram represents the synchronous contraction cycle in the whole excised Fallopian tubes and uterus. The letters V, M, F and N on the ordinate refer to "vigorous," "moderate," "feeb'e," or "no" muscular contractions respectively.

THE INFLUENCE OF TEMPERATURE ON THE RHYTHM OF THE ISOLATED HEART OF THE YOUNG CHICK EMBRYO

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Introduction

It is well known that the chick heart first begins to beat when the embryo is about 30 hours old and when nine to ten pairs of somites have developed. The first pulsations are localized, weak, spasmodic twitches that do not involve the whole heart wall, and some time elapses before a regular rhythm is established. The rhythm, at first slow, gradually increases in strength and frequency during the next fifty hours. Since the sympathetic nerve fibres do not reach the heart until the fifth day (Lillie, 1908), its beat is not dependent, up to that time at least, on any nervous mechanism. It is a purely muscular affair and as such lends itself readily to experimental studies on the behavior of heart muscle, as distinguished from muscle-nerve preparations. Although the hearts from 48- and 72-hour embryos are scarcely a millimeter in diameter, they can be readily cut out and isolated *in vitro* long before nerve connections are established. Such isolated hearts will continue to pulsate at room temperature for many hours in simple Locke solution. The rate is dependent upon a number of environmental conditions, such as temperature, carbon dioxide tension, hydrogen-ion concentration, salt content, and other conditions of the medium, and upon mechanical stimulation, etc. Throughout the present series of experiments a Locke solution containing 0.9 per cent NaCl, 0.042 per cent HCl, 0.024 per cent

$CaCl_2$, and 0.02 per cent $NaHCO_3$, with a pH of about 7.2, was used. The amount and depth of the fluid and the presence or absence of a cover make considerable differences in the rate of the heart beat. If, for example, a heart is placed in a drop of Locke solution in the bottom of a slide-well (15×3 mm.), the rate at 26° C. may be 72 per minute with the cover on and only 52, 40, or 32 with the cover off. Similar differences were noted when hearts were examined in Petri dishes (50×10 mm.). The deeper the fluid the faster the rate became when the cover was off, and with the cover on the rate became still faster. These changes in rate probably depend upon the CO_2 tension.

The most useful method of handling hearts after isolation was in a drop of Locke solution in the bottom of a slide-well (15×3 mm.) with the coverglass on. The embryos were first lifted from the egg to a Petri dish of Locke solution and the heart cut out with a pair of fine scissors and transferred with a pipette to the slide-well. About ninety hearts were utilized; the 2-day old ones (embryos 48 to 53 hours) corresponded to the stages H to I of Patten, the 3-day ones (embryos 69 to 77 hours) corresponded to stages J to K of Patten.

Numerous counts were made of the heart rate immediately after the shell was opened. Those for the 2-day hearts varied from about 120 to 214, and for the 3-day ones, from about 140 to 240 beats per minute. These rates are considerably higher than those given by Preyer, and my average would have undoubtedly been even greater had the eggs been opened in a warm box.

THE HEART AS A WHOLE

Rhythm at Room Temperature, 26° C.—When hearts from 2- and 3-day embryos were cut out and isolated in a drop of Locke solution, as described above, pulsations usually stopped for several minutes, probably because of the shock of the operation and the new environment. They usually started rather suddenly, and at a rate somewhat faster (70 to 80 per minute) than that observed at any subsequent time at room temperature. This rapid pulsation, probably related to the previous period of quiesence, was of short duration, and the rate usually fell from 5 to 15 beats during the next few minutes. This was followed as a rule by a slight slowing during the first hour or two, after which a slight increase often occurred. The rate during the second, third, and fourth hours varied from about 55 to 65 beats per minute, with slight rises and falls. Some hearts varied two or three beats per minute, while others varied as much as ten or eleven beats during this period. With the exception of some of the 2-day hearts, the rate for each individual was surprisingly constant during this four-hour period, in spite of the fact that the heart remained in the same drop of Locke solution in the sealed slide-well. It did not seem to make any difference whether the coverglass was merely laid on or was sealed with vaseline or oil. The metabolism of the beating heart undoubtedly produced changes in the oxygen and carbon dioxide content of the slide-well, but the effect upon the rate, beyond the first decline already noted, was scarcely appreciable during the first four hours. Some of the 2-day hearts, however, showed during the fourth hour marked decrease in the rate and strength of the beats, and occasionally one stopped entirely. Most of them stopped during the fifth hour, but a few continued to beat slowly and feebly for twenty-four hours or more. Three-day hearts did not show such a decline until the fifth, sixth, or seventh hour, and usually continued to beat, though slowly and feebly, for over twenty-four hours. By this time many exhibited atrial pulsations, the ventricle and bulbus remaining quiescent.

Effects of Gradual Increase of Temperature.—Two- and three-day hearts, each in a drop of Locke solution on the bottom of a sealed slide-well, were subjected to a gradually increasing temperature, starting at 22° C. to 27° C. and ending at 39° C. to 40° C. The time required varied from twenty minutes to three hours, and the time elapsing between the isolation of the heart and the beginning of the experiments ranged from twenty-five minutes to five hours. So many variations and irregularities occurred that it is scarcely possible to formulate an absolute rule for the increase in rate with increase in temperature. The average increase in rate per minute for each degree advance in temperature was from 2 to 3 beats at 22° to 24° C.; 4 beats per minute for each degree increase at 24° to 27° C.; 5 to 6 beats per minute at 27° to 29° C.; 7 to 8 beats at 30° to 33° C.; 8 to 10 beats at 33° to 36° C.; and 8 to 12 beats at 36° to 40° C. The maximum rate was occasionally attained at 36°, more often between 37° and 40°, but not infrequently at still higher temperatures. The maximum rate varied from 96 to 200 beats per minute at temperatures up to 40° C. Irregularities such as failure to increase, a sudden decrease, a disassociation in the rhythm of atrium and ventricle, or a complete suspension of the beating frequently occurred.

When the above procedure was repeated on the same heart, the rates at any given temperature usually agreed more closely with each other than with those of another heart at the same temperature. For example, a 3-day heart was subjected to the heating process four times and the rates at 36° were 88, 92, 88, and 92, while another heart of the same age had a rhythm of 148 beats per minute at 36° on the first and second heatings.

The Effect of High Temperature, Above 40° C.—As the temperature increased above 40°, the disassociation in the rhythm of the atrium and ventricle became more common, and the hearts that had not already attained the maximum rate continued to increase. Some of the hearts exhibiting disassociation or heart-block also showed increased rate of both atrium and ventricle up to 46° C. As already noted, the pulsation rate sometimes failed to increase at 36°, but when the upper limit was reached,

whether at 36° or 46°, the rate either remained constant for a period before it declined, began to decline at once, or became irregular. As the beats decreased in number they gradually became weaker and weaker, and finally stopped altogether. Occasionally this stoppage did not occur until the 50° mark.

No especial attempt was made to determine the length of time the hearts could survive the high temperatures. A 3-day heart was exposed for 40 minutes to temperatures ranging from 40° to 47° C. At 41° the rate was 196 per minute; at 42° the atrial rate was 200 and the ventriculo-bulbar rate 100; at 45° the atrial rate was 240 and the ventriculo-bulbar rate 120; at 46° the atrial rate was 252 and the ventriculo-bulbar rate irregular and intermittent; at 47° the atrial rate varied from 224 to 168, while the ventriculo-bulbar rate showed long rest periods and short active periods with a rapid rhythm. When removed to room temperature all parts of the heart soon began beating synchronously at about 60 per minute; the bulbar contractions were stronger than those of the atrium. After remaining at room temperature for 50 minutes the heart was returned to the warm box at 47.5°, and the rate increased in four minutes from 60 to 180, the bulbar end continuing to beat more vigorously than the atrial. Dissociation in the rhythm of the atrial and ventriculo-bulbar ends then occurred,—the pulsations of the atrial end decreased irregularly in number, during the 35 minutes required to raise the temperature to 50° C., became weaker, and stopped; the bulbar pulsations became intermittent, a long rest period was followed by a short active one of 10 to 18 seconds with rapid strong beats, and these beats likewise stopped at 50° C. Within a minute the heart was removed to room temperature where it pulsated slowly and weakly for an hour, the bulbar end continuing the longer. With most of the hearts the atrial end survived longer than the bulbar.

Heart-Block.—We have already noted that dissociation in the rate of the atrium and ventricle, or heart-block, frequently occurs when hearts are subjected to rising temperature. Sudden change from room temperature to 38° or 39° C. likewise frequently produces this effect, as shown by the following experiments. The isolated heart from a 3-day embryo, after beating regularly at the rate of 92 per minute at 27° C., was transferred to the warm box at 38° C. Three minutes later the atrium was pulsating at 120 and the ventriculo-bulbar part at 12 per minute. One minute later the rates were 148 and 74. The heart was removed to room temperature and after ten minutes the whole heart was beating synchronously at 92 per minute. It was again transferred to the warm box, where the rate gradually increased to 156 per minute during the next ten minutes, with no indication this time of heart-block. As it was cooled down again to 27°, the rate of the whole heart gradually decreased to 96 per minute.

Another isolated heart from a 3-day embryo, after pulsating regularly, 34 per minute for thirty minutes at 21° C., was put into the warm box at 38.5°. Three minutes later the rate was 84; five minutes later 132; two minutes later the atrial rate was 132 and the ventriculo-bulbar rate 84, slowly changing to 140 and 76, respectively. Three minutes after returning to room temperature, 22° C., the various parts of the heart were beating synchronously at 60 per minute, which slowly dropped to 12 per minute in twenty minutes. After changing to fresh Locke solution it was transferred again to the warm box. For three or four minutes the heart beat synchronously at increasing rates and then suddenly exhibited block. The atrial rate varied during the next twenty minutes from 96 to 120 and occasionally became irregular. The ventriculo-bulbar rate, on the other hand, suddenly dropped to 20, decreasing thereafter, and in 10 minutes had stopped entirely. Shortly after transfer to room temperature, 22° C., the whole heart was beating synchronously at 30 to 40 per minute.

Heart-block occasionally occurred at lower temperatures. A 3-day heart, which was beating regularly at 40 per minute at 25° C., was transferred to a warm box at 26°, in which the temperature was rising at the rate of one degree every one to three minutes. Between 28° and 29° the ventriculo-bulbar rhythm suddenly dropped to 8, the atrial rhythm remaining at 64. As the temperature increased, the ventriculo-bulbar rhythm increased, at first more rapidly than the atrial, until it became one half that of the latter. For example, at 33° the atrial was 80, the ventriculo-bulbar 40; at 38° the atrial was 120, the ventriculo-bulbar 60; at 42° the atrial was 132, the ventriculo-bulbar 70; at 43.5° the atrial was 152, and the ventriculo-bulbar 76. As the temperature ranged from 44° to 45° there were slight variations in the atrial rate, from 144 to 152, and great variation in the ventriculo-bulbar rate. Sometimes the ventriculo-bulbar part beat with the atrium, sometimes at one-half its rate, changing frequently and suddenly from one rate to the other.

Sometimes the ventriculo-bulbar end may stop beating entirely when the temperature is suddenly changed. A 3-day heart was beating regularly at 48 per minute at 26° C. Four minutes later it was put into the warm box (39.4° C.); the rate rapidly increased during the first two minutes to 120. One half minute later the atrial end was beating at the rate of 120, while the ventriculo-bulbar end stopped suddenly. The rate of the atrial end gradually increased during the next two minutes to 132 beats per minute, the ventriculo-bulbar end remaining quiescent. The preparation was then removed to room temperature (26° C.). As the heart cooled the rate dropped to 96 and the whole heart began beating synchronously for a minute; the ventriculo-bulbar end stopped for four minutes, and then began to beat synchronously with the atrium at 40 per minute.

Two-day hearts exhibited similar dissociation of atrial and ventriculo-bulbar rhythm. One heart that had been beating for over an hour at 40 per minute at 22.5° was put into the warm box and the temperature raised about one degree per minute. At 38° the heart rate was 152 per minute. The beats then became somewhat irregular, and at 39° the atrial rate was 168 and the ventriculo-bulbar rate 84; at 40° the rates were, respectively, 172 and 86, the ventriculo-bulbar pulsating synchronously with every alternate beat of the atrium. A minute after return to room temperature (22.5°), the whole heart was pulsating synchronously at 140, and sixteen minutes later the rate had dropped to 36 per minute.

Not infrequently, when the atrial and ventricular rates were dissociated, the latter showed in addition an intermittent type of rhythm; that is, an active period of varying length with fairly rapid pulsations, followed by a period of complete rest, varying in length in different hearts and in the same heart at different times. This intermittent type of rhythm occurs much more frequently when the atrium, ventricle, and bulbus are completely separated from one another, as will be shown later on.

Dissociation between atrium and ventricle and ventricle and bulbus, where each part beats at a different rate, sometimes occurred at high temperatures. A three-day heart, at 47° to 48° C., had an irregular atrial rhythm varying from 120 to 144 per minute; the ventricle showed only occasional weak beats, the bulbus, on the other hand, beating intermittently and irregularly for periods of ten to eighteen seconds, each period being followed by a long rest period often of a minute or more. The number of beats during the periods of activity varied from 32 to 44 for the 10-second period to 60 for the 18-second period, an unusually rapid rate for the bulbus. In addition, the bulbar contractions were much stronger than usual. At 48.5° the entire heart had regained synchronous pulsation with a rate of 120 per minute, and the bulbar end was still beating more strongly than the atrial. As the temperature increased, the rate decreased to an occasional beat at 50°, at which temperature it soon stopped entirely. After transference to room temperature the whole heart pulsated feebly for about an hour, the bulbar pulsations persisting longest, which was unusual, as the atrial end is generally more resistant to high temperatures.

The heart-block of the clinicians, whether partial or complete, is supposed to be due to injury to the atrio-ventricular conduction bundle. These very young embryonic hearts contain no such bundle, but show direct muscular continuity between the three parts of the heart. When the hearts are contracting slowly at 20° to 25° C. the contraction wave can be easily followed under the binocular microscope as it passes from the atrial to the bulbar end. When partial or complete block is produced by increased temperature, it is often difficult to determine the exact place at which the change in rate occurs, as the pulsating atrium produces more or less movement of the adjoining part of the ventricle; but presumably block always occurs at the atrio-ventricular junction, as there is a fairly sharp anatomical boundary between them. This will become more apparent in the next section of this article, in which the separated atrium, ventricle, and bulbus are treated as individual units.

Since the heart-block always disappeared when the hearts were brought back to room temperature, it is evident that no serious injury, if any at all, occurred at the atrio-ventricular or the ventriculo-bulbar junction. The fact that the ventricle and bulbus exhibited an intermittent type of rhythm often, and the atrium rarely or never, supports the assumption which these experiments on heart-block seem to indicate, viz., that there are physiological differences between the muscles of the atrium, the ventricle, and the bulbus.

Although increase in temperature appears to be the immediate cause of the heart-block, it is evident that other factors in the environment are more important, since in the egg the heart beats synchronously at 39.5° C. The physiological differences of its three parts are emphasized by the environmental conditions.

SEPARATED ATRIUM, VENTRICLE, AND BULBUS ARTERIOSUS

That the inherent rates of pulsation of the atrium and ventricle are different may be inferred from the work of Burrows (1912) on the cultivation of embryonic chick-heart muscle *in vitro*. He found that explants from the atrium beat faster than those from the ventricle. Recently Johnson (1924) has shown, in a beautiful series of experiments in which fine ligatures were tied around the bulbo-ventricular and atrio-ventricular junctions of two-, three-, and four-day chick hearts *in situ*, that the rhythm of the atrium is faster than that of the ventricle, and that of the ventricle faster than that of the bulbus when the impulses from atrium to ventricle and ventricle to bulbus are blocked by the above procedure. It is possible to show this same inherent difference by dividing the isolated heart with a pair of fine scissors at the atrio-ventricular and ventriculo-bulbar junctions into three separate parts —atrium, ventricle, and bulbus. The separated parts, lying side by side in the same solution, show very marked differences in their rhythmicity.

Rhythm at Room Temperature.—At room temperature (25° to 27° C.) the following records may be taken as examples of the rates of these three parts—atrium, ventricle, and bulbus (A, V, B)—under the conditions indicated. In each experiment the embryo was transferred from the egg to a Petri dish of Locke solution, and the heart cut out and transferred with a drop of the solution to the bottom of a slide-well (15×3 mm.). Records of the rate of the whole heart were taken with coverglass on and off. It was again transferred to a Petri dish of Locke

solution, cuts were made across the atrio-ventricular and bulbo-ventricular junctions to effect complete separation, and the three parts returned in a drop to the slide-well, where the pulsation rates were observed with coverglass on and off. The increased rate with the coverglass on, due presumably to the increased CO_2 tension, is quite apparent for the whole heart and for the separated atrium, but less so for the ventricle and bulbus.

No. 77.

2-day heart—slide-well—Locke solution pH. 7.2

9.55 A. M. the egg was opened and the heart cut out
10.00 A. M. rate of whole heart 52 per min., coverglass on
10.06 A. M. rate of whole heart 48 per min., coverglass on
10.11 A. M. rate of whole heart 36 per min., coverglass off
10.12 A. M. rate of whole heart 54 per min., coverglass on
10.16 A. M. rate of whole heart 36 per min., coverglass off

	A.	V.	B.	separated, in fresh drop
10.18 A. M.				
10.21 A. M.	52	24 int.	0	per min., coverglass on
10.36 A. M.	48	23	10 ir.	per min., coverglass on
10.50 A. M.	45	22	8 ir.	per min., coverglass on
11.15 A. M.	41	22	7 ir.	per min., coverglass on
12.07 P. M.	36	22	10 ir.	per min., coverglass on
12.34 P. M.	40	26	12	per min., coverglass on

No. 73.

2-day heart—slide-well—Locke solution pH. 7.2

9.45 A. M. the egg was opened and the heart cut out
10.06 A. M. rate of whole heart 0 per min., coverglass off
10.07 A. M. rate of whole heart 60 per min., coverglass on
10.10 A. M. rate of whole heart 60 per min., coverglass on
10.11 A. M. rate of whole heart 46 per min., coverglass off
10.14 A. M. rate of whole heart 60 per min., coverglass on

	A.	V.	B.	separated, in fresh drop
10.18 A. M.				
10.21 A. M.	44	0	0	per min., coverglass off
10.23 A. M.	54	0	0	per min., coverglass on
10.24 A. M.	52	21	1	per min., coverglass on
10.31 A. M.	52	20	10	per min., coverglass on
12.20 P. M.	48	3	0	per min., coverglass on

No. 78.

3-day heart—slide-well—Locke solution pH 7.2

11.00 A. M. the egg was opened and the heart cut out
11.07 A. M. rate of whole heart 0 per min., coverglass off
11.09 A. M. rate of whole heart 46 per min., coverglass off
11.10 A. M. rate of whole heart 62 per min., coverglass on
11.12 A. M. rate of whole heart 74 per min., coverglass on
11.34 A. M. rate of whole heart 74 per min., coverglass on
11.35 A. M. rate of whole heart 40 ir. per min., coverglass off
11.37 A. M. rate of whole heart 38 ir. per min., coverglass off

	A.	V.	B.	separated, in fresh drop
11.38 A. M.				
11.42 A. M.	44 ir.	11	0	per min., coverglass off
11.57 A. M.	74	10	0	per min., coverglass on
12.14 P. M.	74	10	0	per min., coverglass on
12.30 P. M.	72	10	0	per min., coverglass on

No. 72.

3-day heart—slide-well—Locke solution pH 7.2

2.25 P. M. the egg was opened and the heart cut out
2.38 P. M. rate of whole heart 62 per min., coverglass on
2.40 P. M. rate of whole heart 48 per min., coverglass off
2.41 P. M. rate of whole heart 60 per min., coverglass on
2.42½ P. M. rate of whole heart 48 per min., coverglass off
2.45 P. M. rate of whole heart 58 per min., coverglass on

	A.	V.	B.	separated, in fresh drop
2.48 P. M.				
2.51 P. M.	68	0	0	per min., coverglass off
2.53 P. M.	64	0	0	per min., coverglass off
2.55 P. M.	76	10	4	per min., coverglass on
3.04 P. M.	80	16	0	per min., coverglass on

From these and other experiments it is perfectly evident that, for several hours at least, the atrium always beats faster than the ventricle, and the ventricle faster than the bulbus. The rate of the atrium approaches closely that of the entire heart—it may be more or less rapid or about the same. The rate of the ventricle, on the other hand, is usually less than one half that of the atrium for the two-day, and considerably less than that for the three-day hearts. Ventricles from three-day hearts fail to pulsate more often than do those from the two-day ones. The ventricular rhythms are more apt to be irregular than the atrial; this was also noted by Johnson in his ligature experiments. The pulsations of the bulbus often fail entirely, are usually few in number (1 to 12 per minute) when they do occur, and as a rule come at irregular intervals. They are less frequent in the three-day than in the two-day hearts.

It is quite evident that the fast rate of the ventricle and bulbus in the intact heart is dependent upon the stimulus from the atrium, and that when separated the two structures show less spontaneity in older stages than in younger ones. In other words, the muscles of the ventricle and bulbus tend to lose their spontaneous rhythmicity with age.

Effect of Gradual Increase of Temperature.—When the isolated atrium of the 2-day heart was subjected to a gradually increasing temperature, the increase in rate of the atrium resembled that of the intact isolated heart, except that the changes were not quite so regular. From 25° to 28° or 29° the increase per minute per degree was about 4 beats; above 29° the increase usually exceeded this, and from 35° to 40° the increase per minute per degree anywhere from 0 to 36 beats. The most rapid rate noted at 38° was 158, at 40° 180, and at 41° 204. The lowest at 39° was 108. The rate may decrease or become irregular after 38°, but the intermittent character so common in the ventricle was not noted.

The behavior of the isolated ventricles was erratic and varied greatly. Sometimes the pulsation rate increased more or less irregularly, without going into the intermittent type of rhythm, from 0 to 24 beats per minute at room temperature to 60 to 90 per minute at 39° to 40° C. The rate of increase per minute per degree increase was more variable than with the entire heart. Sometimes there was no increase for a degree or two, or a decrease occurred. In general, however, the ventricles that reached a rate of 60 to 90 per minute at 39° to 40° showed greater increases per minute per degree at temperatures above 35° than at temperatures below 30°. The rate of the ventricle was usually less than half that of the atrium at corresponding temperatures. Many of the ventricles showed

but little increase as the temperature rose. As an example, the following figures indicate the number of pulsations per minute for each degree from 25° to 34° inclusive: 18-4-16-16-20-8-13-14-14-23, intermittent at 35°. Sometimes there was an actual decrease in the rate and even complete cessation of pulsation as the temperature increased. This was more frequent with the three- than with the two-day hearts.

The intermittent type of rhythm, which almost every ventricle exhibited sooner or later when subjected to rising temperature, was characterized by an active period of pulsation, followed by a period of rest. The length of these periods and the number of pulsations varied in the different hearts and in the same heart at different times and at different temperatures.

The following examples will serve to elucidate the intermittent rhythm of ventricles from two-day hearts. The first at 36° C. had an active period of 35 seconds with 30 beats, followed by a rest period of 30 seconds, then a single beat followed by another rest period of 10 seconds. As the temperature increased to 37° there was an active period of 27 seconds with 33 beats, followed by a rest period of 30 seconds, then a single beat and another rest period of 10 seconds; at 38°, active period 15 seconds with 22 beats, rest period 35 seconds; at 39°, active period 10 seconds with 16 beats, rest period 35 seconds. Another heart (No. 28) at 39° had an active period of 15 seconds with 19 beats, followed by a rest period of 30 seconds. Heart No. 42 at 40° had an active period of 30 seconds with 48 beats, followed by a rest period of 25 seconds. When such ventricles were returned to room temperatures, the intermittent character of the rhythm usually disappeared and the pulsations became fairly regular. When again returned to higher temperatures the intermittent rhythm usually returned, but with different periods and rates.

As the temperature rose, some of the bulbi, which did not beat at room temperature, showed occasional beats (1 to 4 per minute), but the number per minute at any time, even in those that were beating at room temperature, rarely exceeded 15 at any temperature, and frequently an increase of temperature produced no increase in rate. The pulsation rate was usually irregular and often intermittent in character. The intermittent types were even more variable than the ventricular ones. The bulbus from a two-day heart (No. 7), for example, at 38° had an active period of 20 seconds with 16 beats and a rest period of 90 seconds; at 39° it had an active period of 14 seconds with 8 beats and a rest period of 26 seconds. Another at 36° C. had an active period of 15 seconds with 6 beats, followed by a rest period of 100 seconds.

SUMMARY

Two- and three-day embryonic chick hearts, after isolation from the embryo, exhibit fairly regular automatic pulsations for several hours at room temperature in Locke solution. Since the nerve fibres do not reach the heart until the fifth day, the contractions are purely myogenic in nature.

The pulsation rate varies in different hearts at 26° C. from about 40 to 80 per minute.

If the temperature is gradually increased, the rate increases about 4 beats per minute up to 29° or 30°, from 4 to 8 per minute from 30° to 35°, and from 4 to 20 per minute from 35° to 40°. The increases are rarely regular and not infrequently the rate remains constant for a degree or two, or even drops temporarily.

At temperatures above 29° C. these hearts frequently exhibit block, more often between atrium and ventricle than between ventricle and bulbus. During the period of heart-block the ventricular rhythm is usually half or less than that of the atrium, and when the hearts are returned to room temperature synchronous pulsations return, indicating that no serious injury has occurred to the muscular connection between atrium and ventricle or to the ventricular muscle itself. The heart-block seems to signify physiological differences between the muscle of the atrium and that of the ventricle, which are emphasized by the environment.

When the atrium, ventricle, and bulbus are isolated from one another by cutting them apart, they exhibit marked differences in rhythm, which again indicates physiological differences. At room temperature (26° C.) the atrial rate approaches closely that of the entire heart; the ventricular rate is usually less than one-half that of the atrium, frequently much less; while the bulbar rate is much less than the ventricular, and not infrequently the bulbus fails entirely to pulsate or does so irregularly.

When the atrium is subjected to increasing temperature, the increase in rate resembles that of the intact isolated heart. The ventricles vary; sometimes the rate goes up fairly regularly, but usually becomes irregular and often intermittent, i. e., a period of active pulsation is followed by a period of rest. The bulbus is still more variable. The rhythm is usually irregular and frequently intermittent, and when regular rarely exceeds 15 per minute.

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A CASE OF POLYCYTHAEMIA VERA WITH SPECIAL REFERENCE TO THE FAMILIAL FEATURES AND TREATMENT WITH PHENYLHYDRAZINE*

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Introduction

This case of polycythaemia is of interest for several reasons, namely: that the symptoms were neurological; that the disease was discovered in another member of the family without symptoms; and that phenylhydrazine was used as the only treatment other than rest in bed. A rather detailed history and physical examination is given because of the presence of the typical signs in a marked degree, and also of some smaller interesting changes (especially in the extremities and finger-nails) not noted elsewhere.

History.—The patient, a man aged 46, was seen first on December 10, 1923, complaining of numbness and weakness of his right arm and leg.

This symptom came on while standing up talking to a friend on July 28, 1923. He noticed first that his right arm had gone to sleep with marked tingling. This was followed in a few moments by a similar sensation in the right leg. There was no loss of motion. After sitting down for five minutes it all passed off. A little later it returned again when he stood up. He always has found that standing perfectly still caused aching pain in the back. This time there also was tingling around his mouth, his tongue felt twisted, and articulation became difficult. After walking some distance the sensation passed off again only to recur later in the day. Vision was always unimpaired and speech merely made awkward, but he was never unable to talk. He stayed in bed for two weeks before going to the mountains for a month. While there he had frequent tingling in the little finger of the right hand but no other symptoms. About October 1, 1923, he tried working again but found that he became so easily fatigued that he rested another month. He then attempted work for two weeks. At that time after coming home, feeling very tired, another attack of the difficulty in speaking occurred. Little by little this became rather less.

The onset of the disease in this patient is difficult to determine. His complexion has always been very red and the conjunctivitis has been present since childhood. For the ten years that he has been married his wife knows that he has always looked the same, with variations in degree on some days. For at least ten years he has had aching pain in the back and in the long bones. He often feels that he is "getting the grippe." Standing still for any length of time always brings on these pains. The pain in the feet is of an itchy character as in chilblains, the ends of the fingers, toes and the heels feeling much over-filled.

There has also been at times a sense of fullness in the left flank in the region of the spleen. Frequently oppressive frontal headaches have occurred early in the morning. Occasionally he has suffered from shooting pains in the jaws and for a short time there was deep-seated pain in the left orbit and tenderness over the left frontal sinus. These were made worse by lying down.

Family History.—Father died at 62 years of cancer of stomach. Mother died at 45 years of pneumonia. Both parents are said to have had very florid complexions. Four sisters and one brother; none have headaches. No history of heart disease, tuberculosis or general familial disease could be obtained.

His *previous history* contained some interesting points. He was subject to headaches, which, from the age of 19 to 35, were so severe that he would have to go to bed for 48 hours. Sometimes a little transient blurring of vision was associated with them. These migraine-like headaches have become less severe at present. Has had aching pains in his bones for years which are usually worse at night. Malaria for two years when 12 years old. No recurrence. Since childhood his eyes have always been inflamed, lids thickened, reddened and irritable. He had tonsillitis as a young man. Teeth decay easily. He has had no diseases of the cardio-respiratory system. He had chronic appendicitis requiring removal of the appendix nine years ago. There was no history of haematuria, or other haemorrhages. He had a soft chancre in 1908, and was given mercury and salvarsan at intervals for four years. His Wassermann reaction has always been negative since. He was married in 1914, but his wife has had no pregnancies. He is of rather a high strung temperament, a moderate user of alcohol and tobacco and does not take much outdoor exercise.

Physical Examination.—Man of slight build. Height 5 feet 9 inches. Weight 113 pounds. Has never weighed more than 125 pounds. According to his calculated ideal weight he was 46 pounds underweight. There was no peculiarity in the proportions of the skeletal structure. One was immediately struck by the intense red color of the face and with the great number of dilated venules over the cheeks, especially on the malar eminences, bridge of nose, ears and down on to the neck. It gave him almost a strawberry appearance. He recounts that on two occasions there was spontaneous rupture of a venule on the cheek with bleeding for a few moments. The hands and feet were also of a dark red color, especially the palms and soles. This redness did not extend above the wrist but ended rather abruptly just at the joint line on the ventral surface, and a little above this level on the dorsal surface. There was rather marked sweating of the hands and feet. On many days while under observation the whole skin of the trunk had a diffuse red blush very similar to a scarlatinaform eruption. On any irritation, this blush would come out and when pressure was applied, there was momentary pallor followed by increase redness. The skin of the chest showed a few spidery angiomata and numerous fine superficial vessels in the upper portion.

The eyelids were slightly thickened at the edges and considerably reddened. The conjunctivae of the lids were engorged

* This case is reported through the courtesy of Dr. Thomas R. Boggs.

and the vertical blood vessels dilated. The sclerae were fairly clear. The veins over the temples were engorged and tortuous. The pupils reacted normally. The color of the retinae did not seem increased but the veins were very full, almost black and very slightly tortuous. No haemorrhages were seen. The physiological cups were normal.

The lips were purplish-red and the gums much increased in color and spongy. It is to be noted that this engorgement was more marked below the level of the alveolar processes and it was only there that the dilatation of the vessels was seen forming a rich network over the whole floor of the mouth and extending to the buccal surface of the mucous membrane. The largest of these small vessels were arranged vertically. The soft palate, fauces and mucous membrane of the pharynx were very vascular. No pigmentation of the mucous membrane was seen. There was no enlargement of any of the lymphatic glands. The lungs were clear. The heart was very slightly larger than normal. Action and sounds were normal. The pulse was normal in every respect and the wall of the radial artery was just palpable. Blood pressure 150/80. The spleen could be felt about two centimeters below the costal margin. It was firm but not tender. Liver edge just felt at costal margin. No haemorrhoids. Genitalia normal. The neurological examination by Dr. Henry M. Thomas revealed no abnormality. The muscular strength was uniformly good; the superficial and deep reflexes normally active and equal on the two sides. No sensory disturbance discovered.

The blood examination on December 11, 1923, demonstrated R. B. C. 9,700,000; W. B. C. 7,520. Hb. 120 per cent (Sahli) and a differential count of 68.5 per cent P. M. N.; 26.5 per cent lymphocytes; 5 per cent L. M. T. In the smear the red blood cells were of normal size and shape but of a very dark color.

Among the laboratory tests, the cerebrospinal fluid pressure was 150 millimetres of water. It was clear and colorless but contained 23 red blood cells per cubic millimetre. The Wassermann and the colloidal mastic tests were negative. The blood Wassermann was negative. The patient's blood was a Type III according to the Moss grouping. The urine all through the period of observation had a slight trace of albumin but never any red blood cells or casts except as noted below. The specific gravity varied between 1.005 and 1.022. The phthalein excretion was 55 per cent in two hours. The blood non-protein-nitrogen was 45.8 mgm. per 100 c.c., blood creatinine 1.6 mgm. per 100 c.c. and blood uric acid 4.37 mgm. per 100 c.c. The basal metabolism has often been found considerably raised in these cases, but in this patient it was quite normal, namely, —2. Testing the fragility of the red cells demonstrated haemolysis beginning at 0.48 and complete at 0.22, the control having the respective figures of 0.42 and 0.32.[3]

DISCUSSION

Undoubtedly a heredo-familial trend exists in many cases of polycythaemia. Nichanin[2] cites a case in a young woman whose mother and sister had enlarged spleens and cyanosis. The present patient's mother and father both had very florid complexions. The mother's complexion apparently aroused comment which was in great part due to myriads of dilated venules over the face. She also suffered considerably from headaches and died of pneumonia at 45 years of age. It therefore is possible that she had polycythaemia. I had an opportunity to examine one brother, five years younger and one sister three years younger than the patient. The brother was of larger build than the patient, complained of no special symptoms but had many venules in the skin of the face and on the ears. The spleen was not palpable. The red blood count was 6,120,000, W. B. C. 7,250, and haemoglobin 110 per cent. There was nothing else important found. The sister had no physical signs similar to those of the patient. Her blood count was: 4,300,000 R. B. C., 8,250 W. B. C. and 92 per cent haemoglobin. Two other sisters had blood counts done elsewhere, both in the neighborhood of 90 per cent haemoglobin and 4,500,000 red cells. Neither had symptoms of much interest. Many dilated venules were present over the face on one, who complained of general aches and pains.

In studying this disease the patient alone does not give the necessary material, but if it were feasible to examine all the relatives, near and distant, I feel sure that many would be found to have the characteristic blood picture, and the conclusion would be reached that it is a familial disease directly inherited. It is equally common in either sex, and occurs probably in the early years of life. A striking illustration of the association of polycythaemia with hereditary disease is that given by Doll and Rothschild.[3] They reported the case of a man of 44 who, suffering from hereditary chorea (Huntington's), had to stop work because of the nervous symptoms, mainly slow articulation and beginning dementia. He was found to have an enlarged, hard spleen, a haemoglobin of 115 (Sahli) with R. B. C. 6,500,000 and W. B. C. 6,500. There was urobilinuria. This patient was one of six children of whom five had chorea. Of the three who were available for examination, two had a definite polycythaemia (one with splenomegaly), while the other was on the borderline. All had urobilinuria. Engelking[4] examined a whole family in which the disease was present in three generations. Five of the last generation and the mother and grandmother in addition were affected. The oldest of the children was 19 years of age. Together with the polycythaemia, a most important point emphasized, corroborating the view of the dependence of the disease on some defect in the germ plasm, is the occurrence of infantilism in all these children, and in the older members disturbances in the functions of some of the glands of internal secretion. I do not mean to suggest that one might draw the conclusion that the polycythaemia itself is caused by, or in any way connected with, an endocrinopathy, but that, given a germ plasm whose various developmental physiological functions may become so unbalanced as to produce a certain combination of changes resulting in a disequilibration of the endocrine glands ending in the picture of infantilism with which we are fairly familiar, it is logical and easily conceivable that these same functions may become unbalanced in a different combination to produce abnormalities in the haematopoietic functions such as erythraemia and leukaemia. This might depend

on environmental factors of which we have no inkling at present.

The hyperhydrosis of the hands and of the feet is a very constant finding and I know of no satisfactory explanation. A possible plausible reason for this phenomenon may be that in these most peripheral situations the actual circulation is slower than elsewhere; the fingers look and feel distended, the skin is stretched and in an inadequate attempt at reducing the local volume of blood a reflex stimulation of the sweat glands takes place. It was noted that in our patient this occurred most frequently during the times when he complained of pain and fullness of the parts with subjective and objective sensation of increased local heat. Besides this hyperhydrosis, more or less localized in this way, the hands and feet are also redder than other parts except the face. The skin of the palms and soles is more highly colored than the dorsal surfaces and this coloring does not usually extend above the wrist but ends rather abruptly just at the wrist-joint on the ventral surface and a little above this level on the dorsal surface. I have noticed this delimitation in many cases. The finger-nail beds, I believe, have a characteristic appearance. Running longitudinally in different lengths there is a pink ribbon-streaking effect to be seen in some or all of the fingers. The ribbons of increased color vary from fine lines to bands a millimeter or a millimeter and a half in width. The fingers may or may not be actually clubbed, but it is common for the nails themselves to be considerably rounded if the disease has continued to be severe for long. It is very usual to see the palms and soles literally dripping wet in spite of the fact that the epidermis in both areas often seems thickened.

It is not the purpose to discuss here the possible pathological-physiological process which results in this picture of an intense overactivity of the bone-marrow. Treatment may aim either to depress the bone-marrow, or to increase the rate of blood destruction. The use of phenylhydrazine for the latter purpose has given a few interesting results. Morawitz and Pratt[5] used the drug to produce experimental anaemia in animals and the suggestion of its possible value in the treatment of polycythaemia is well worth consideration and trial. Eppinger and Kloss[6] first gave it subcutaneously in doses of 10 c.c. of a 5 per cent solution. Later, administration by mouth was found satisfactory. They noted the reduction in haemoglobin and red cell count with an occasional leucocytosis.

Taschenberg[7] gives a detailed account of the use of the drug in a case of erythraemia with splenomegaly with low blood-pressure and also severe symptoms of haemorrhages and pulmonary infarcts. For a year and a half the patient was given periodic treatment with varying amounts, from 2.4 grams during seven days, up to three and four times that dose. Taschenberg observed that each time there was need of further treatment the more it was necessary to give in order to obtain a fall in the counts. On several occasions both haemoglobin and red cells were reduced to normal. During the process the patient usually became slightly jaundiced, and the urine became black in color on standing. A severe anaemia of 30 per cent Hb. and one million red cells developed after the giving of 2.4 grams in six days. There was also a leucopenia of 3500 with 77 per cent polymorphonuclear cells and 19 per cent lymphocytes. At other times there was a leucocytosis. In Taschenberg's opinion a special mechanism was aroused by a repetition of the use of the drug, so that the red cells exhibited an increased resistance not necessarily to hypotonic salt solution but specifically to phenylhydrazine.

Treatment

Our patient was given phenylhydrazine hydrochloride 0.1 gram in a capsule by mouth every day in the manner shown in Table I.

TABLE I.

Date 1924	Doses of phenylhydrazine	Haemoglobin	R. B. C.	W. B. C.	Remarks
1/ 7	.....	145%	7,612,000	8,000	.....
1/ 8	0.1 gm.	148%	8,696,000	5,600	.....
1/ 9	0.1 gm.	145%	10,816,000	6,600	.....
1/10	0.1 gm.	135%	10,144,000	7,000	.....
1/11	0.1 gm.	138%	8,912,000	6,600	.....
1/12	0.1 gm.	138%	9,904,000	8,200	.....
1/13	0.1 gm.	135%	8,640,000	7,600	.....
1/14	0.2 gm.	132%	8,176,000	8,200	.....
1/15	0.1 gm.	130%	8,192,000	9,800	.....
1/16	0.2 gm.	135%	8,224,000	8,000	.....
1/17	0.1 gm.	130%	8,096,000	9,000	.....
1/18	0.2 gm.	130%	7,768,000	11,000	.....
1/19	0.1 gm.	130%	7,884,000	9,600	.....
1/20	0.1 gm.	128%	6,900,000	7,400	.....
1/21	0.1 gm.	130%	7,416,000	8,000	.....
1/22	0.1 gm.	128%	6,736,000	9,000	.....
1/23	0.2 gm.	125%	7,304,000	11,000	Phlebitis
1/24	.....	125%	6,776,000	12,000	.....
1/25	0.1 gm.	122%	6,944,000	12,000	.....
1/26	.....	121%	6,565,000	10,000	.....
1/27	0.1 gm.	121%	7,152,000	11,000	.....
1/28	.....	120%	6,850,000	10,520	.....
1/29	0.1 gm.	118%	6,530,000	11,320	.....
1/30	.....	118%	6,225,000	9,120	.....
1/31	0.1 gm.	116%	6,325,000	10,120	.....
2/ 1	.....	114%	6,125,000	12,350	Haematuria
2/ 2	.....	112%	6,050,000	10,420	.....
2/ 3	.....	100%	5,000,000	13,800	.....
2/ 4	.....	98%	4,856,000	14,600	.....
2/ 5	.....	90%	4,064,000	15,800	.....
2/ 6	.....	85%	4,096,000	10,600	.....
2/ 8	.....	80%	4,760,000	16,000	.....

TABLE I.—Continued.

2/ 9	.....	85%	4,232,000	19,800	.....
2/11	.....	85%	4,784,000	10,000	Myelocytes
2/13	.....	80%	4,000,000	13,000	.....
2/14	.....	75%	3,490,000	11,000	.....
2/15	.....	72%	3,176,000	13,000	.....
2/18	.....	75%	3,680,000	14,600	.....
2/22	.....	78%	3,964,000	11,000	.....
2/26	.....	85%	4,464,000	7,800	.....
3/1 (on discharge)		90%	4,792,000	8,200	.....

There was no gastric disturbance noted at any time. Since the blood count was not diminished very rapidly and no unpleasant symptoms developed after six days, he was given an extra 0.1 gram every other day. He felt fairly well except for his usual frontal headache and pains in the muscles and joints. The differential count at the end of the week was P. M. N. 72 per cent, Lymphocytes 23 per cent, L. M. N. 3 per cent, and Eosinophiles 2 per cent. By January 18th the haemoglobin was definitely falling and there was improvement in the symptoms. The aching pains were better. The spleen was increasing in size, however, and its rather tender, firm edge could be felt about 4.5 cm. below the costal margin. The differential count showed a slight increase in the polymorphonuclear cells to 78 per cent. The urine was of a very dark amber color and on standing became almost black, as a result of the excretion of the drug. On January 23rd a phlebitis of the internal saphenous vein began, which lasted about five days with some fever. By the 31st of January the red cells and haemoglobin were coming down slowly. On the 1st of February red cells were found in the urine in moderate numbers. The drug was discontinued. At this time the patient was greatly improved subjectively and objectively. He had been free from headache for two weeks and the full, oppressive sensation had entirely disappeared. The conjunctivae were much paler and the color of the gums and lips was within normal limits. The enlarged vessels in the mucous membranes previously mentioned could no longer be easily distinguished. The spleen was less tender and a little smaller. Six days later the blood destruction was still going on. The differential count of the 15,800 leucocytes showed 87 per cent polymorphonuclear cells. The lowest point the blood reached was on February 15th, fifteen days after the last dose of the total 2.4 grams given. The 13,000 leucocytes showed 79 per cent polymorphonuclear and 20 per cent mononuclear cells. There were several myelocytes in the smear. The fragility test at this time showed absolutely normal figures. The patient did not feel weak but had occasional pain in the toes. The phlebitis had subsided, and he had gained eight pounds since admission. The conjunctivitis had disappeared. On February 24th he had a great deal of pain in the toes with marked perspiration of the parts. The color was quite normal.

He was discharged on the first of March feeling much better in every way. The differential count still showed 83 per cent polymorphonuclears, but otherwise the blood was normal. The spleen was just palpable, firm, but not tender.

On April 9th we heard from him again. He felt much better, had gained 17 pounds, and the red cells were 5,300,000. On April 23rd his haemoglobin was 110 per cent, R. B. C. 5,688,000, W. B. C. 11,800, with 88 per cent polymorphonuclears.

By the end of May he began to have a return of his aches and pains and a little weakness of his arm again. On May 29th his blood was up to 120 per cent Hb. and 6,850,000 R. B. C. He was started on another course of phenylhydrazine in 0.1 gram doses. His subsequent counts are shown in Table II.

TABLE II.

Date 1924	Doses of phenylhydrazine	Haemoglobin	R. B. C	W. B. C.	Remarks
4/ 9	.....	.....	5,300,000	.....	.....
4/23	.....	110%	5,688,000	11,800	88% P.M.N.
5/29	0.1 gm.	120%	6,850,000	.....	.....
5/30	0.1 gm.	.....	.....	.....	.....
5/31	0.1 gm.	112%	6,720,000	8,500	.....
6/ 1	0.1 gm.	.....	.....	.....	.....
6/ 2	0.1 gm.	.....	.....	.....	.....
6/ 3	0.1 gm.	105%	6,000,000	7,800	.....
6/ 4	.....	.....	.....	.....	.....
6/ 5	0.1 gm.	.....	.....	.....	.....
6/ 6	.....	105%	6,400,000	8,100	.....
6/ 7	0.1 gm.	.....	.....	.....	.....
6/ 9	0.1 gm.	100%	5,600,000	7,800	.....
6/11	0.1 gm.	.....	.....	.....	.....
6/13	.....	97%	5,360,000	8,200	.....
6/17	.....	90%	4,640,000	8,900	.....

The plan for further treatment is to have the blood counted regularly every two weeks for some time, and to give 0.1 gram doses frequently enough to maintain the blood at a constant level. In this way he may take a dose once or twice every week or two.

Because of Taschenberg's experience that repeated treatment usually needs increasing total doses, it was very satisfactory to observe the reduction of the blood to normal a second time with only one gram of the drug.

It is too early yet to draw many conclusions as to the ultimate usefulness of phenylhydrazine in the disease. However, from this case one can say that it offers a very definite prospect of keeping the blood count near the normal level. Its selective action on the red cells marks a great advantage over benzol. The latter's tendency to cause a dangerous leucopenia is well recognized, of course, and the leucocytosis that appeared during the first administration of the phenylhydrazine is distinctly comforting. It is supposed that the action is exerted elsewhere

than in the bone-marrow and causes merely an increased destruction of cells; nevertheless, the fact that the leucocytosis occurs, with myelocytes frequently among them, make one feel that we cannot yet rule out a direct action on the bone-marrow.

SUMMARY

1. A case of polycythaemia vera, with neurological symptoms, is described and certain minor physical findings pointed out.

2. The disease is a familial one and every case should be investigated from this point of view. There may be other familial defects present also.

3. Treatment with phenylhydrazine hydrochloride by mouth has been very encouraging so far and seems to hold out hopeful prospects for keeping the disease in check. No unpleasant symptoms from the drug were noticed, although a slight phlebitis and a transient haematuria of minimal proportions occurred.

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NOTES ON NEW BOOKS

The Common Neuroses: Their Treatment by Psychotherapy. By T. A. Ross, M. D., F. R. C. P. E., Medical Director, Cassel Hospital for Functional Nervous Disorders. $4.20 net. *(New York, Longmans, Green & Co.; London, Edward Arnold & Co., 1923.)*

Dr. Ross, for seventeen years in general middle-class practice, and during that time and since then especially interested in the care of psychoneuroses, gives in this book a commonsense statement of his experience and methods. His expressions of indebtedness show in a way the trend of his training. At first he had decided enthusiasm for the Weir-Mitchell treatment, which, however, wore off after a few disappointments. His first personal tribute goes to Dr. Williamson of Ventnor, who "taught him how to speak to nervous patients," next to Dr. Henry Head, who showed him "a new light in a very dark hour" and "became the real author of any psychological knowledge which the writer of this book may possess." He was ultimately inspired by the work of Dejerine whose valuable book, translated by Jelliffe, is indeed an interesting account of his and Dubois' experience. He expresses his indebtedness to

Dr. James K. Walsh for his "too little known book on Psychotherapy," and to Dr. A. F. Hurst for the repeated demonstration of his methods of removing hysterical symptoms. And there is no doubt that the influence of the Freudian school, although very much mitigated, plays an important rôle in the final presentation of the topic.

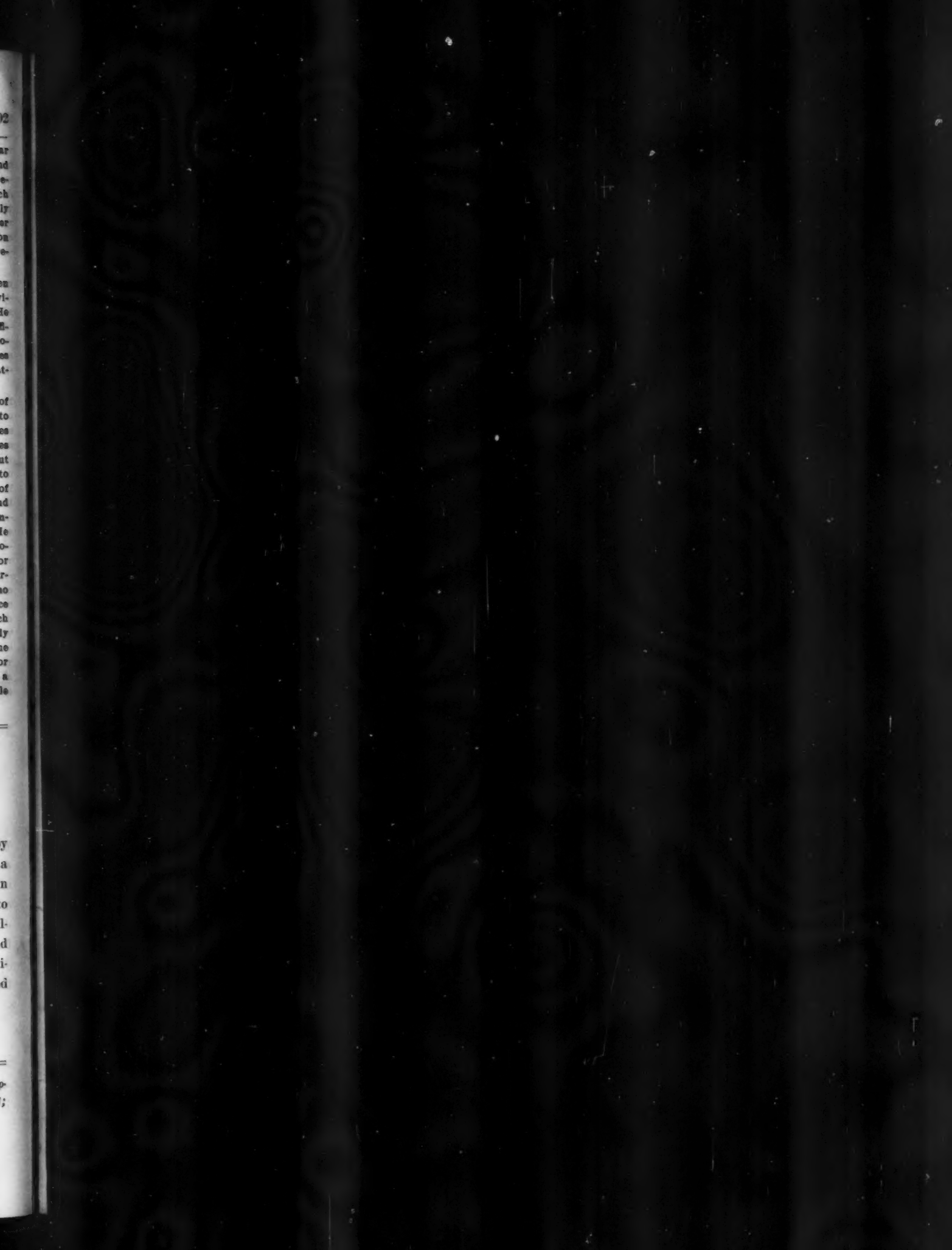
In a brief theoretical introduction, and in an initial chapter on etiology and psychological conception, Dr. Ross leads us from the Weir-Mitchell rest cure and its exhaustion theory, over the reflex theory with its emphasis on eye and pelvic disorders, to a discussion of the emotional disturbances (such as fainting at the first sight of an operation, vomiting from disgust, fear, with its tremor and visceral effects), the conditioned reflex, and the unconscious mental processes (illustrated by the post-hypnotic suggestion). After this brief analysis he passes to a classification of the psychoneuroses into three types of reaction to difficulties;—(1) by over-reaction; (2) by under-reaction, or by failure to react at all; (3) by pretending that the difficulty is not present. This suggests to him the classification into neurasthenic disorders, hysterical disorders, and disturbances through obsession and compulsion, the compulsion neuroses. Pages 27 to 155 are devoted to the description and treatments of neurasthenia. The descriptive statements are relatively short. The main stress is laid on a very lucid statement of the procedure of treatment: the first interview and the thorough examination and early stages of the treatment, and gradually the study of the emotional part of the condition. In the special chapter on the treatment of those patients who improve and relapse, Ross gives a description of the method of free association. In the chapter on the residual symptoms he discusses the causes for incomplete recoveries and leads over to the chapters on the Freudian method. Ross considers anxiety as the fundamental fact in neurasthenia, and his treatment is one of uncovering the anxieties which produce the various reexacerbations and arousals of symptoms. He discloses the underlying emotional setting with the help of free association, advising the physician to sit behind the patient, and the patient to relax his limbs and to close his eyes. While Freudian analysis attempts to disclose the contents of the whole unconscious, Ross attempts to get back of the time when the Symptoms first appeared and back to the original provocative situation. Only when the condition resists this kind of modified symptomatic analysis does he consent to go further into an actual Freudian analysis. This would consist in the analysis of dreams, of which he gives a few very simple examples. He also discusses the transference, i. e., as a rule, the identification of the physician with the father image, and he discusses the problems rather in terms of anxiety than in terms of conflict. The persistence of residual symptoms may finally have to be laid to the existence of a special constitution or diathesis. In a special chapter on the Freudian method Ross offers some advice and strictures and some criticisms which deserve to be borne in mind by the general practitioner and those not specifically trained in psychoanalysis. He denies the existence of the so-called true neurasthenia of Freud, or what is called the "actual neurosis," as a distinguishable entity.

The hysterical reaction is covered in forty-eight pages. He discusses amnesias, fugues, somnambulism, double personality, trances, deliria, hysterical or emotional attacks, and hallucinations. He next takes up the sensory and motor and visceral symptoms. The examination needs to be full and accurate, but must leave no signs of indecision and is best accompanied by a simple but firm remark that the sort of thing found "is common" and not something startling. Probably from his war experience Ross considers the hysterical easily suggestible and open to cures which savor of the miraculous. A rapid removal of the symptoms brings out an anxiety condition which may require more radical treatment. He warns especially against the tendency to consider suicidal threats altogether harmless. He also appears to be opposed to the abreaction method, the encouragement of emotional display in the rehearsal of the causal or conditioning episodes.

The compulsion or obsessional neuroses obtain only scant ten pages of discussion. They too are closely related to the evidently fundamental neurasthenic and anxiety pattern. He recognizes the compulsion neuroses as certainly the most difficult of all the neuroses, and warns in the main against psychoanalytic attempts in the face of the fact that Ernest Jones considers these cases especially amenable to just such treatment.

The last chapter is made up of a "note on the treatment of the manic-depressive psychoses." This brings the reviewer to a point of considerable regret about Ross's attitude. He makes a very decided contrast between the neuroses and the psychoses and deplores all talk of "borderland cases" (justly, but without making it unnecessary), and with the English tendency to speak of lunatics and of asylums, and of the inaccessibility of these cases to psychotherapy, he creates an injudicious and incorrect contrast which largely drops away with our non-dogmatic conception of minor and major psychoses. He claims that he never has seen a neurasthenic develop a psychosis, which is not probable and not good doctrine either for physicians or for the general public. It looks as if neurasthenia could be a fixed entity about which there would be no mistakes or alternatives. One can give adequate reassurance without throwing too gloomy a view on the psychoses, which frequently are much less disorganizing individually and socially than many psychoneuroses. Apart from this, the book is one deserving of a very strong recommendation to any student or physician, as a simple, lucid, conservative statement of a strongly mitigated Freudian technique and easily intelligible elementary outline of management of cases. A. M.

NOTICE OF MEETING

The Inter-State Post-Graduate Assembly, directed by the Tri-State District Medical Association, extends a hearty invitation to the physicians of America who are in good standing in their State or Provincial Societies to attend the annual assembly, which is to be held at Milwaukee, Wisconsin, October 27th, 28th, 29th, 30th and 31st, five full days of post-graduate work. Many eminent members of the profession and citizens have accepted places on the program.

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